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Serum 1,5-anhydro-D-glucitol levels predict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study

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ABSTRACT

Objective: Serum 1,5-anhydro-D-glucitol (1,5-AG) is well-known to be a useful clinical marker of both short-term glycemic status and postprandial hyperglycemia. In addition, previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test is a risk factor for cardiovascular diseases (CVD). However, no previous prospective study has reported the association between serum 1,5-AG levels and the risk of CVD. In this study, we examined whether serum 1,5-AG levels can predict the incidence of first-ever CVD.

Methods: Our study was a population-based cohort study in an urban area of Japan. Study subjects comprised 2095 initially healthy Japanese (991 men and 1104 women, mean age: 58.5 years) with no history of coronary heart disease (CHD) or stroke. They were followed up for an average of 11.1 years, and 147 CVD events (64 CHD and 83 strokes) were observed.

Results: The adjusted hazard ratios (HRs) of all CVD in men increased linearly ($p = 0.004$). The HR in the category with serum 1,5-AG levels of 14.0 μg/mL or less was 2.22 (95% confidence interval; 1.24–3.98) compared to the reference category (24.5 μg/mL or greater). Similar results were also shown with a sensitivity analysis in non-diabetic men. Conversely, no significant relationship between serum 1,5-AG levels and CVD risks was observed in women.

Conclusions: Our results suggest that measurement of serum 1,5-AG levels is useful to detect individuals, especially men, at higher risk for CVD, regardless of the presence or absence of diabetes.

1. Introduction

Serum 1,5-anhydro-D-glucitol (1,5-AG) levels are well-known to rapidly decrease concomitantly with the excretion of glucose in urine, and serum 1,5-AG is a useful clinical marker for short-term glycemic status and postprandial hyperglycemia [1–3].

Previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test (OGTT) is a risk factor for cardiovascular diseases (CVD) [4,5]. A randomized controlled trial of individuals with impaired glucose tolerance also reported that acarbose, an α-glycosidase inhibitor that suppresses the elevation of postprandial glucose levels, reduced the incidence of CVD as well as type 2 diabetes [6]. These findings suggest that detection and improvement of postprandial hyperglycemia is important for CVD prevention.

An OGTT is useful for the detection of postprandial hyperglycemia, however, it requires overnight fasting, long time, additional costs, and is not always feasible in routine clinical settings or during health check-ups. In contrast, measurement of serum 1,5-AG levels can be performed using a single non-fasting blood sample, relatively costs less, and may be an alternative to OGTT. However, to our knowledge, no previous prospective study has shown the association between serum 1,5-AG levels and the risk of CVD in initially healthy individuals. We examined whether serum 1,5-AG levels can predict the incidence of first-ever CVD in a population-based cohort study of an urban area in Japan.

2. Methods

2.1. Study design and samples

The details of the Suita study have been described elsewhere [7–9]. Briefly, the Suita study is a prospective population-based cohort study of an urban area in Japan. In 1989, 6485 Suita city residents (age, 30–79 years) were randomly sampled and enrolled as study participants. They underwent medical examinations every 2 years. Among these participants, 2406 participants underwent medical examinations between April 1994 and February 1995, and their serum samples were collected and stored at −80 °C. In this

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study, we measured serum 1,5-AG levels in these stored samples. Of these 2406 participants, 289 were excluded from the present analysis for the following reasons: history of coronary heart disease (CHD) or stroke ($n=78$), lost to follow-up ($n=132$), serum creatinine level of 176.8 mmol/L (2.0 mg/dL) or more ($n=4$), and data missing ($n=97$). Finally, the remaining 2095 participants (991 men and 1104 women) with serum 1,5-AG measurements were included as subjects in the baseline study and were followed up until December 31, 2007. Informed consent was obtained from all subjects, and the institutional review board at the National Cerebral and Cardiovascular Center approved this study.

2.2. Baseline data collection

The baseline survey included questionnaires, anthropometric measurements, and blood sample tests. Height and weight were measured in light clothing, and body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Blood pressure was measured 3 times in more than 1-min intervals by well-trained physicians in a sitting position after at least 5 min of rest, using a standard mercury sphygmomanometer [7], and the third measurement of blood pressure was adopted for the present analyses. The levels of total serum cholesterol, high-density-lipoprotein (HDL)-cholesterol and creatinine were determined using an automatic analyzer in the laboratory of the National Cerebral and Cardiovascular Center. Estimated glomerular filtration rates (eGFR) were estimated with a following equation for the Japanese: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ (×0.739: if women) [10].

2.3. Measurement of 1,5-AG

In 2009, stored frozen serum samples were shipped to the clinical laboratory company for measurement of 1,5-AG (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). 1,5-AG was measured using the enzymatic method with the "Determiner L 1,5-AG" measurement kit manufactured by the Kyowa Medex Co., Ltd. (Tokyo, Japan) and an H7700 Clinical auto-analyzer, manufactured by the Hitachi High-Technologies Corporation (Tokyo, Japan). The coefficient of variation was less than 5%.

2.4. Ascertainment of outcomes

Outcome ascertainment has been previously described elsewhere [7–9]. The main outcome is the incidence of first-ever CVD events (stroke and CHD). Physicians or nurses checked the health status of each subject at biennial clinical visits to the National Cerebral and Cardiovascular Center, and all participants also completed yearly questionnaires by either mail or telephone. The patients suspected of developing stroke or CHD were confirmed by a review of medical records performed by either the registered hospital physicians or the cohort study research physicians. In addition, to complete the surveillance, we also conducted a systematic search of death certificates for fatal stroke and MI. In Japan, all death certificates are forwarded to the Ministry of Health, Welfare, and Labor and coded for the National Vital Statistics.

A stroke was defined according to criteria from the US National Survey of Stroke [11]. Classification of stroke subtypes (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) was based on the examination of computed tomographic scans, magnetic resonance images, or autopsies (subarachnoid hemorrhages were excluded from the present analyses). With regard to myocardial infarction (MI), definite and probable MI were defined according to the criteria of the MONICA project [12]. The criteria for CHD were first-ever MI, coronary angioplasty, coronary artery bypass grafting and sudden cardiac death.

2.5. Statistical analysis

A previous report from Japan proposed a serum 1,5-AG level of 14.0 μg/mL, irrespective of sex, as the cut-off for the diagnosis of diabetes [13]. The distribution of serum 1,5-AG levels differed between sexes. Accordingly, we adopted a serum 1,5-AG level of 14.0 μg/mL as the lower cut-off in common, and set the median of those who had serum 1,5-AG of more than 14.0 μg/mL as the upper cut-off (overall and according to sex), overall: 23.1 μg/mL, men: 24.5 μg/mL, women: 21.3 μg/mL. These cut-offs were used to compare baseline characteristics, crude incidence rates, and hazard ratios (HRs). To calculate p values for continuous variables, one-way analysis of variance was used, and for categorical variables, Chi-square test was used. To compare in women the prevalence of medication for diabetes and current alcohol drinking status, Fisher's exact test was used. The p values to test for a linear trend in HRs were calculated.

A Cox proportional hazard model was used to estimate age- and multivariate-adjusted HRs with 95% confidence intervals (CIs). The HRs were adjusted for the following baseline covariates as follows for model 1, age; for model 2, model 1 plus BMI, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication), hypercholesterolemia (total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication) [14], HDL-cholesterol, eGFR, current cigarette smoking (non-current and current) and current alcohol drinking (men; non-current/light to moderate/heavy, women: non-current/current);, for model 3, model 2 plus diabetes (fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL), postprandial plasma glucose (PPG) ≥11.1 mmol/L (200 mg/dL), or use of anti-diabetic medication). Fasting was defined as fasting time of 8 h or more ($n=1401$, 67%), and postprandial was defined as that of less than 8 h ($n=694$, 33%). We defined current alcohol drinking as non-current drinking, light to moderate drinking (alcohol consumption of less than 46 g/day), or heavy drinking (that of 46 g/day or more). However, because women with heavy alcohol drinking were few ($n=8$, 0.7%) and had no CVD incidence, we treated current alcohol drinking as non-current/current drinking in the multivariate analyses of women. Menopause was added to model 2 and model 3 in women. Combined analyses of women and men adjusting for sex were conducted only in CHD and ischemic strokes because significant interactions between sex and serum 1,5-AG levels were observed in all CVD ($p=0.03$) and all strokes ($p=0.01$).

In addition, three sensitivity analyses were conducted: First, similar analyses were performed in non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL). Second, the definition of postprandial in the diagnostic criteria for diabetes was changed to a fasting time of 2 h or less (postprandial: $n=28$, 1%), and similar analyses were conducted to confirm the influence of diabetes diagnostic criteria by PPG. Third, adjustment for waist circumferences in model 2, instead of BMI, was conducted to estimate the influence of insulin resistance. We did not enter both BMI and waist circumferences into the models to avoid the colinearity problem because waist circumferences highly correlated with BMI (correlation coefficient: 0.84). In addition, triglycerides levels were categorized by tertile and added to the model 2 in the combined analysis of women and men with fasting time of 8 h or more ($n=1401$), and similar analyses for CHD and ischemic strokes were conducted.

All p values were two-tailed, and $p<0.05$ was considered statistically significant. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, Carolina, USA).

3. Results

The mean (standard deviation) of serum 1,5-AG was 23.0 μg/mL (9.2) in men and 20.0 μg/mL (7.0) in women. The overall dis-

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Table 1
Baseline characteristics by sex and serum 1,5-anhydro-D-glucitol levels, the Suita study, Japan, 1994–2007.

	Men			
	1,5-Anhydro-D-glucitol (μg/mL)			*p*
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	423	416	152	
Age (years)	58 (12)	61 (12)	63 (11)	<0.001
Body mass index (kg/m^2)	22.7 (2.7)	22.8 (2.9)	23.1 (2.9)	0.24
HDL cholesterol (mmol/L)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	0.48
1,5-Anhydro-D-glucitol (μg/mL)	31.3 (5.6)	19.7 (3.0)	8.8 (3.6)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (15.6)	78.1 (16.0)	79.0 (18.1)	0.19
Hypertension (%)[a]	32	37	45	0.01
Hypercholesterolemia (%)[b]	23	23	21	0.85
Diabetes (%)[c]	0	3	30	<0.001
Current cigarette smoking (%)	44	39	41	0.36
Alcohol drinking (non/light to moderate/heavy) (%)	29/53/18	29/55/16	35/47/18	0.55
Hypertension medication (%)	13	15	20	0.09
Hypercholesterolemia medication (%)	4	4	5	0.81
Diabetes medication (%)	0	0	20	<0.001
	Women			
	1,5-Anhydro-D-glucitol (μg/mL)			*p*
	≥21.3	14.1–21.2	≤14.0	
Number of subjects	442	438	224	
Age (years)	59 (12)	55 (12)	58 (12)	<0.001
Body mass index (kg/m^2)	22.2 (3.2)	21.9 (2.7)	22.3 (3.2)	0.12
HDL cholesterol (mmol/L)	1.6 (0.4)	1.6 (0.3)	1.6 (0.3)	0.001
1,5-Anhydro-D-glucitol (μg/mL)	26.7 (4.1)	18.0 (2.0)	10.5 (3.2)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (19.7)	81.2 (16.8)	81.1 (15.2)	0.71
Hypertension (%)[a]	33	26	31	0.06
Hypercholesterolemia (%)[b]	39	37	38	0.80
Diabetes (%)[c]	1	1	12	<0.001
Current cigarette smoking (%)	11	8	8	0.42
Current alcohol drinking (non/light to moderate/heavy) (%)	75/25/0	72/27/1	72/28/0	0.31
Menopause (%)	76	63	71	<0.001
Hypertension medication (%)	14	12	17	0.17
Hypercholesterolemia medication (%)	7	7	5	0.46
Diabetes medication (%)	0	0	4	<0.001

Mean (standard deviations), or percentage is shown. GFR means glomerular filtration rate.
[a] Hypertension is defined by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.
[b] Hypercholesterolemia is defined by total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication.
[c] Diabetes is defined by fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) in those with fasting time of 8 h or more, postprandial plasma glucose ≥11.1 mmol/L (200 mg/dL) in those with fasting time of less than 8 h, or the use of antidiabetic medication.

tribution (minimum, 25th percentile, median, 75th percentile, maximum) of serum 1,5-AG by sex was 1.2, 17.0, 23.1, 28.9, and 55.3 μg/mL, respectively in men, and 1.7, 15.2, 19.8, 24.8, and 41.5 μg/mL, respectively in women (data not shown). The prevalence of diabetes and medication for diabetes at baseline was highest in the category with the lowest serum 1,5-AG (≤14.0 μg/mL) in both sexes, and was much higher in men (Table 1). Age and prevalence of hypertension increased as serum 1,5-AG decreased in men only.

During the follow-up period (11.1 years average), 147 CVD events (64 CHD and 83 strokes) were observed. The CHD included 14 percutaneous coronary angioplasty, 5 coronary artery bypass grafting, 1 sudden death, 41 myocardial infarctions and 3 unclassified CHD. The strokes included 53 ischemic strokes, 14 hemorrhagic strokes and 16 unclassified strokes. The incidence rates of all CVD and each CVD subtype increased as 1,5-AG levels decreased in men, and the incidence rate of all CVD was 15.1 per 1000 person-years in the lowest 1,5-AG category (Table 2). In model 2, there was a statistically significant linear increase in the adjusted HRs of all CVD in men ($p = 0.004$), and the adjusted HR was 2.22 (95% CI 1.24–3.98) in the lowest 1,5-AG category. In model 3, the adjusted HR of all CVD in the lowest 1,5-AG category was less than model 2. However, the adjusted HR of the middle category (14.1–24.4 μg/mL) was not very different and the elevation of risk was still significant, 1.74 (95% CI 1.07–2.84). In men, similar results were observed for each CVD subtype, although the HRs of CHD were much lower than of all strokes and were not statistically significant. In women, similar results were not observed, although, for CHD, similar trends were observed (Table 3). In the combined analysis of women and men for CHD, the HRs in model 2 increased linearly with decrease in serum 1,5-AG levels ($p = 0.03$), and the adjusted HR in the lowest 1,5-AG category was 2.10 (95% CI 1.10–4.02) (Table 4).

A sensitivity analysis for non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL) showed that the adjusted HRs for all CVD in model 2 increased as 1,5-AG levels decreased ($p = 0.03$), and the adjusted HR was 2.00 (95% CI 0.88–4.55) in the lowest 1,5-AG category (Table 5). Similar results were observed with all strokes and ischemic strokes, but such a relationship was not clear in CHD.

In the sensitivity analyses, altering the definition of postprandial, entering waist circumferences or adding triglycerides levels to the models hardly alter the results. In addition, waist circumferences or triglycerides levels were not related with the risk for CVD or each CVD subtype.

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Table 2
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in men, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥24.5	14.1–24.4	≤14.0	
Person-years	4727	4322	1455	
All cardiovascular diseases				
Cases, *n*	26	49	22	
Incidence rates/1000 person-years	5.5	11.3	15.1	
Model 1[a]	1	1.76 (1.09–2.86)	2.29 (1.29–4.07)	0.003
Model 2[a]	1	1.79 (1.10–2.91)	2.22 (1.24–3.98)	0.004
Model 3[a]	1	1.74 (1.07–2.84)	1.72 (0.89–3.34)	0.049
Coronary heart disease				
Cases, *n*	16	19	10	
Incidence rates/1000 person-years	3.4	4.4	6.9	
Model 1[a]	1	1.21 (0.61–2.38)	1.81 (0.81–4.05)	0.17
Model 2[a]	1	1.14 (0.57–2.25)	1.59 (0.70–3.59)	0.29
Model 3[a]	1	1.13 (0.57–2.24)	1.47 (0.59–3.68)	0.44
All strokes				
Cases, *n*	10	30	12	
Incidence rates/1000 person-years	2.1	6.9	8.2	
Model 1[a]	1	2.56 (1.25–5.25)	3.02 (1.31–7.01)	0.006
Model 2[a]	1	2.64 (1.28–5.45)	3.32 (1.41–7.79)	0.003
Model 3[a]	1	2.53 (1.23–5.23)	2.29 (0.87–6.01)	0.04
Ischemic strokes				
Cases, *n*	8	20	9	
Incidence rates/1000 person-years	1.7	4.6	6.2	
Model 1[a]	1	2.16 (0.95–4.92)	2.84 (1.09–7.37)	0.02
Model 2[a]	1	2.15 (0.94–4.93)	2.86 (1.09–7.49)	0.03
Model 3[a]	1	2.10 (0.92–4.82)	2.28 (0.78–6.67)	0.09

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, model 3: adjusted for model 2 plus diabetes.

4. Discussion

This is the first report of a prospective cohort study showing that serum 1,5-AG levels predict CVD incidence in men, similar to HbA_{1c} [15–17] or postload glucose levels in OGTT [4,5]. More subjects with overt diabetes were included in the category with serum 1,5-AG levels of 14.0 μg/mL or less, which would lead to the greatest risk. Those with serum 1,5-AG levels of 14.1 to 24.4 μg/mL, whose preva-

Table 3
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥21.3	14.1–21.2	≤14.0	
Person-years	5077	5293	2424	
All cardiovascular diseases				
Cases, *n*	22	15	13	
Incidence rates/1000 person-years	4.3	2.8	5.4	
Model 1[a]	1	0.83 (0.43–1.60)	1.23 (0.62–2.44)	0.68
Model 2[a]	1	0.92 (0.47–1.79)	1.30 (0.65–2.60)	0.54
Model 3[a]	1	0.91 (0.47–1.77)	1.04 (0.48–2.22)	0.99
Coronary heart disease				
Cases, *n*	7	5	7	
Incidence rates/1000 person-years	1.4	0.9	2.9	
Model 1[a]	1	0.82 (0.26–2.60)	2.09 (0.73–5.96)	0.21
Model 2[a]	1	0.89 (0.28–2.83)	2.33 (0.81–6.71)	0.15
Model 3[a]	1	0.87 (0.27–2.76)	1.74 (0.54–5.56)	0.42
All strokes				
Cases, *n*	15	10	6	
Incidence rates/1000 person-years	3.0	1.9	2.5	
Model 1[a]	1	0.83 (0.37–1.86)	0.83 (0.32–2.14)	0.65
Model 2[a]	1	0.93 (0.41–2.09)	0.88 (0.34–2.27)	0.77
Model 3[a]	1	0.92 (0.41–2.08)	0.75 (0.26–2.12)	0.59
Ischemic strokes				
Cases, *n*	6	7	3	
Incidence rates/1000 person-years	1.2	1.3	1.2	
Model 1[a]	1	1.48 (0.50–4.41)	1.03 (0.26–4.12)	0.84
Model 2[a]	1	2.01 (0.66–6.11)	1.20 (0.29–4.89)	0.60
Model 3[a]	1	1.99 (0.66–6.06)	1.01 (0.22–4.71)	0.71

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL-cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, menopause, model 3: adjusted for model 2 plus diabetes.

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Table 4
Incidence rates and adjusted hazard ratios for coronary heart disease and ischemic strokes by serum 1,5-anhydro-D-glucitol levels in men and women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥23.1	14.1–23.0	≤14.0	
Number of subjects	854	865	376	
Person-years	9606	9814	3878	
Coronary heart diseases				
Cases, *n*	22	25	17	
Incidence rates/1000 person-years	2.3	2.5	4.4	
Model 1[a]	1	1.36 (0.76–2.44)	2.17 (1.14–4.13)	0.02
Model 2[a]	1	1.41 (0.78–2.52)	2.10 (1.10–4.02)	0.03
Model 3[a]	1	1.37 (0.76–2.46)	1.76 (0.85–3.63)	0.12
Ischemic strokes				
Cases, *n*	19	22	12	
Incidence rates/1000 person-years	2.0	2.2	3.1	
Model 1[a]	1	1.25 (0.67–2.31)	1.58 (0.76–3.27)	0.22
Model 2[a]	1	1.24 (0.67–2.31)	1.56 (0.75–3.24)	0.23
Model 3[a]	1	1.21 (0.65–2.25)	1.23 (0.54–2.82)	0.56

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, sex, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

lence of diabetes or anti-diabetic medication was clearly lower than those with 14.0 μg/mL or less, also had significantly elevated risks. This suggested the possibility that many subjects without overt diabetes who had postprandial hyperglycemia with excretion of glucose in the urine were included in this middle category. Measurement of serum 1,5-AG levels can be useful to detect individuals at greater risk for CVD even among those without overt diabetes. In fact, the sensitivity analyses in non-diabetic subjects with almost normal plasma glucose levels also showed similar results, which reinforced these findings.

In men, the relationship between serum 1,5-AG levels and stroke was much clearer than that with CHD. The prevalence of hypertension increased with decrease in serum 1,5-AG levels, but the prevalence of hypercholesterolemia did not change, irrespective of serum 1,5-AG levels. Such discrepancies in the relationships between serum 1,5-AG levels and risk factors for CVD may account for the difference observed between risk of stroke and that of CHD.

In women, no significant relationship was observed between serum 1,5-AG levels and the risk for all CVD or each CVD subtype, although a similar increase in the risk for CHD was found. Previous meta-analyses have shown either that women with diabetes have a higher risk for CHD than men with diabetes [18,19], or that there was no sex difference [20]. The DECODE study also showed that the HR of death from CVD in individuals with 2-h glucose levels of 11.1 mmol/L or greater tended to be higher among women than among men [5]. The present results show an opposite sex difference, and the reason is not clear. However, the prevalence of diabetes at baseline was much lower in women than in men, and the incidence rate of all CVD and each CVD subtype was also relatively lower in women. Such discrepancies in basic characteristics

Table 5
Sensitivity analyses of incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in non-diabetic men with fasting or postprandial plasma glucose levels of less than 6.1 mmol/L, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	388	349	77	
Person-years	4326	3636	703	
All cardiovascular diseases				
Cases, *n*	22	40	8	
Incidence rates/1000 person-years	5.1	11.0	11.4	
Model 1[a]	1	1.75 (1.04–2.96)	1.65 (0.73–3.72)	0.07
Model 2[a]	1	1.76 (1.04–2.98)	2.00 (0.88–4.55)	0.03
Coronary heart diseases				
Cases, *n*	14	17	2	
Incidence rates/1000 person-years	3.2	4.7	2.8	
Model 1[a]	1	1.26 (0.62–2.57)	0.71 (0.16–3.15)	0.96
Model 2[a]	1	1.18 (0.57–2.43)	0. 86 (0.19–3.86)	0.89
All strokes				
Cases, *n*	8	23	6	
Incidence rates/1000 person-years	1.8	6.3	8.5	
Model 1[a]	1	2.58 (1.15–5.79)	3.11 (1.07–9.00)	0.01
Model 2[a]	1	2.51 (1.11–5.66)	3.68 (1.26–10.75)	0.01
Ischemic strokes				
Cases, *n*	7	15	5	
Incidence rates/1000 person-years	1.6	4.1	7.1	
Model 1[a]	1	1.97 (0.80–4.85)	3.05 (0.96–9.69)	0.045
Model 2[a]	1	1.92 (0.77–4.75)	3.45 (1.08–11.05)	0.03

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

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between men and women might result in the sex difference. In addition, the involvement of selection bias cannot be completely eliminated in women. Further studies with sufficient samples and CVD events in women are necessary to clarify this problem.

Measurement of serum 1,5-AG levels could detect not only those with persistent hyperglycemia but also those with transient postprandial hyperglycemia who are likely to be at higher risk for development of diabetes in the near future. Accordingly, decrease in serum 1,5-AG levels might be related with the elevated risk of CVD. The previous epidemiological studies also reported the association of postprandial hyperglycemia with risk of CVD [4–6], and the present results are not inconsistent with them. However, the mechanism remains still inconclusive, and two hypotheses could be considered. First, hyperglycemia itself is a risk for atherosclerotic diseases. Second, hyperglycemia is just a reflection of insulin resistance which is closely related to risk factors for atherosclerotic diseases. In the present study, adjustments for insulin resistance-related factors, waist circumferences or triglycerides, hardly changed the results. This indirectly suggests that serum 1,5-AG levels are independently related with a risk for CVD from insulin resistance, and we infer that hyperglycemia itself might be a risk.

OGTT cannot be conducted easily in the routine clinical setting or during health check-ups because it requires overnight fasting in blood sampling, longer time and extra costs. Conversely, measurement of serum 1,5-AG can be performed easily with a single non-fasting blood sample and is relatively low cost. Serum 1,5-AG levels do not fluctuate very much within an individual if glucose is not excreted into urine; however, it varies widely among individuals [1–3,13,21,22]. Accordingly, periodic measurement of serum 1,5-AG might be important for the early detection of a decrease from the normal level in each individual.

It is also well known that hemoglobin A_{1c} (HbA_{1c}) is useful for the diagnosis of diabetes or as a marker of glycemic control, and elevated HbA_{1c} is associated with increased risk for macro- and micro-complications [15–17,23]. HbA_{1c} can also be measured in a single non-fasting blood sample. However, red cell turnover and hemoglobinopathies influence HbA_{1c} levels, and this has been often identified as a problem [23,24]. In contrast, serum 1,5-AG levels are not affected by red cell turnover and hemoglobinopathies. In terms of screening higher risk individuals among the general population, a combination of HbA_{1c} and serum 1,5-AG measurements might be better choice.

The present analysis had several limitations. First, some aspects of medical history were unknown, including gastric resection, hyperthyroidism and renal glycosuria, which can lower 1,5-AG levels. Second, the present dataset did not include measurement of HbA_{1c} levels or OGTT; therefore, comparison of HbA_{1c} or OGTT with serum 1,5-AG was not possible. Third, a single serum 1,5-AG measurement at baseline may have lead to an underestimation of the association between serum 1,5-AG levels and CVD due to regression dilution bias [25].

In conclusion, the present analyses suggest that in men measurement of serum 1,5-AG was useful to detect individuals at increased risk for CVD, regardless of the presence or absence of diabetes. Measurement of serum 1,5-AG levels might be a useful tool for screening in the clinical setting or during health check-ups. However, this is the first report with a limited population of Japanese, and these findings should be further investigated by studies with sufficient samples and CVD events among various populations, races and geographical areas.

Conflict of interest

None to be declared.

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Importance of cerebral artery risk evaluation before off-pump coronary artery bypass grafting to avoid perioperative stroke

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Abstract

Objective: Cerebrovascular atherosclerotic disease is a widely known risk factor for stroke after conventional coronary artery bypass grafting (CABG). The aim of this study is to evaluate the incidence of stroke in patients with significant cerebrovascular disease after off-pump CABG. **Methods:** In this retrospective study, 611 patients, who underwent off-pump CABG, were divided into high-risk ($n = 196$) and low-risk groups ($n = 415$) for perioperative stroke using preoperative brain magnetic resonance angiography/imaging and cervical Doppler sonography, and the incidence of stroke in the two groups was compared. **Results:** No 'intra-operative' stroke was observed. However, seven patients (3.6%) in the high-risk group and one patient (0.2%) in the low-risk group developed 'delayed stroke' between the day of surgery and postoperative day 18 (mean postoperative day 8.8). The predominant aetiology of delayed stroke was thrombo-embolism. Assignment to the high-risk group had a significant association with the occurrence of delayed stroke ($p = 0.011$). The person-time incidence rate of stroke in the high-risk group was much higher within 1 month (3.57) after CABG than beyond 1 month (0.14). **Conclusions:** Patients with significant cerebrovascular disease did not develop intra-operative stroke after off-pump CABG. However, these patients were likely to suffer from delayed stroke within 30 days of surgery.

Keywords: Coronary artery bypass grafting; Off-pump; Cerebrovascular disease; Stroke

1. Introduction

The aetiology of stroke after coronary artery bypass grafting (CABG) is complex and multifactorial, and it may include systemic inflammatory response, cerebral embolism and cerebral hypoperfusion. Intra-operative release of atherosclerotic emboli associated with aortic cannulation and cross-clamping is believed to be the most important risk factor [1]. Because off-pump CABG can decrease aortic manipulation, this technique has been expected to reduce the incidence of stroke. However, some meta-analyses have failed to demonstrate a significant benefit of off-pump CABG in reducing the rate of perioperative stroke [2,3].

Most previous studies defined stroke as an event occurring over the course of the entire hospital stay and have not focussed on the timing of stroke. More than half of the strokes occurred after the patients fully recovered from the effect of anaesthesia without any neurological deficit [4,5]. The causes of these 'delayed strokes' also seem to be multifactorial, and few studies have specifically addressed the incidence and aetiology of delayed stroke after off-pump CABG.

In addition to cerebral emboli derived from aortic atherosclerosis, patients undergoing CABG are likely to have severe atherosclerosis of the carotid/cranial arteries. The presence of cerebrovascular disease is also a widely accepted risk factor for stroke [6]. The aim of this study was to examine the impact of cerebrovascular disease on the incidence and timing of stroke after off-pump CABG.

2. Materials and methods

2.1. Study group

Between January 1997 and December 2008, 707 patients underwent off-pump CABG in our institution. Among them, 611 patients, who underwent a preoperative screening examination involving brain magnetic resonance imaging (MRI), brain magnetic resonance angiography (MRA) and cervical Doppler ultrasonography, were enrolled in this retrospective study. The 611 patients were divided by neurologists into two groups (high-risk and low-risk) on the basis of the presence or absence of carotid or intracranial artery stenosis and past history of stroke according to an algorithm shown in Fig. 1.

2.2. Surgical techniques

In almost all cases, off-pump CABG was performed through a median sternotomy. Proximal anastomoses of free conduits

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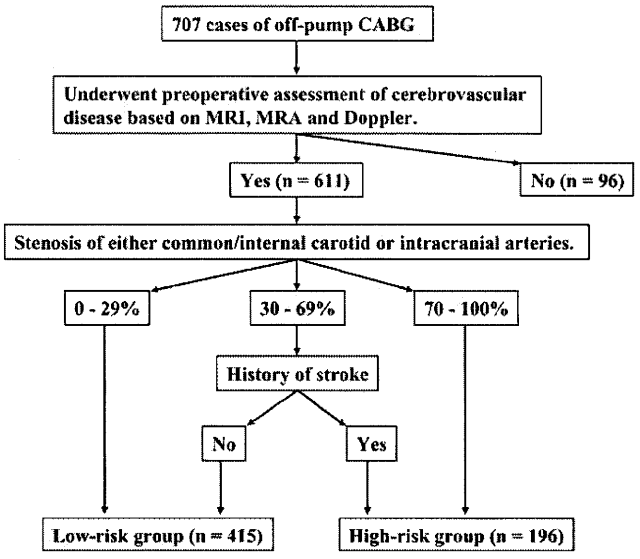

Fig. 1. Algorithm for risk assessment of perioperative stroke after coronary artery bypass grafting. CABG: coronary artery bypass grafting; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

(saphenous vein and radial artery) were placed on the ascending aorta using less invasive anastomotic devices such as Aortic connector (St. Jude Medical Inc., St Paul, MN, USA), Heartstring (Guidant, Indianapolis, IN, USA), and Enclose (Novare Surgical Systems, Cupertino, CA, USA) rather than using a partial aortic clamp. When intra-operative epi-aortic ultrasonography revealed significant atherosclerotic disease, an aortic no-touch technique was applied using the free conduits as Y or I extensions on the *in situ* internal thoracic artery graft (composite graft).

2.3. Perioperative anti-platelet/anticoagulation protocol

The intake of all anti-platelet agents, including aspirin, was suspended 7 days before surgery, except in patients with unstable angina and tight left main disease. Subcutaneous heparin was administered until the day before surgery. During CABG, intravenous heparin was administered to achieve an activated clotting time of greater than 300 s, and it was neutralised at the end of the procedure with protamine sulphate. The administration of aspirin was reinitiated on the day after surgery. Warfarin treatment was also initiated in patients, who had received a vein graft.

2.4. Definitions

Stroke was defined as a new neurological deficit lasting for more than 24 h. If the neurological deficit was present when the patient emerged from anaesthesia, the stroke was defined as 'intra-operative stroke'. 'Delayed stroke' was defined as a stroke occurring after the patient fully recovered from the effect of anaesthesia without neurological deficit and if it occurred within 1 month of surgery. Stroke was diagnosed by neurologists and confirmed by brain MRI or computed tomography (CT). Renal failure was defined as a serum creatinine level of greater than 1.5 mg dl^{-1} or the requirement for haemodialysis. Low cardiac output syndrome (LOS) was defined as the use of postoperative inotropic support for more than 48 h. Perioperative myocardial infarction (PMI) was diagnosed if the level of serum creatine kinase MB isoenzyme was more than 100 IU l^{-1}.

The occurrence of stroke (stroke rate) was expressed as a person-time incidence rate [7]. Incidence per 100 person-months, r, is defined by the following equation: $r = (N/D) \times 100$, where N is the number of strokes occurring during the observation period and D is person-time units (months).

2.5. Statistical analysis

Numerical variables are presented as the mean ± stan-standard deviation for each patient group and compared using the Mann–Whitney test. Categorical variables are given as percentages and compared using the chi-square and Fisher's exact tests where appropriate. Event-free ratio analysis was performed with the Kaplan–Meier method, and statistical significance was calculated with the log-rank test. Univariate analysis, expressed as odds ratio with 95% confidence interval limits and p values, was used to evaluate the effect of preoperative and postoperative variables on the occurrence of neurologic complications. Statistical significance was accepted at $p < 0.05$. Analyses were performed using the SPSS statistical software (version17.0; SPSS Inc., Chicago, IL, USA).

3. Results

Of the 611 patients who underwent the risk assessment for perioperative stroke before surgery, 196 patients (32%) were considered to be at high risk for stroke. None of these patients had experienced a recent episode of cerebrovascular accident (CVA), nor did any of them require previous or concomitant carotid artery intervention. The remaining 415 patients (68%) were considered to be at low risk for perioperative stroke. The preoperative characteristics of the groups are summarised in Table 1. Patients in the high-risk group were older, had a higher prevalence of diabetes and renal failure and a greater average number of diseased coronary vessels. In 423 cases out of the entire 611, off-pump CABG cases, the anastomotic devices were available. Of those, 241 cases used free conduits, and 15.8% of them required aortic no-touch technique after assessment using epi-aortic ultrasonography.

Table 2 lists the observed postoperative results. No intra-operative stroke occurred in either group. However, seven patients (3.6%) in the high-risk group developed delayed stroke after an initially uncomplicated neurologic course, in

Table 1
Preoperative characteristics.

	High-risk (n = 196)	Low-risk (n = 415)	p value
Male	77.0%	79.8%	0.44
Age (years)	69.7 ± 7.6	66.6 ± 9.4	<0.001
Diabetes	54.1%	42.8%	0.009
Renal failure	19.7%	12.0%	0.012
LVEF (%)	59.8 ± 15.6	62.4 ± 14.0	0.10
No. of diseased vessel	2.6 ± 0.6	2.4 ± 0.7	0.001

LVEF: left ventricular ejection fraction.

Table 2
Postoperative results.

	High-risk (n = 196)	Low-risk (n = 415)	p value
LOS	5.6%	4.1%	0.40
PMI	2.6%	4.1%	0.33
Renal failure	32.5%	20.9%	0.002
Episode of Af	22.5%	28.1%	0.15
Intraoperative stroke	0%	0%	
Delayed stroke	3.6% (7 cases)	0.2% (1 case)	0.002
TIA	2.6% (5 cases)	1.2% (5 cases)	0.30
Operative death	1.0%	0.2%	0.24

LOS: low cardiac output syndrome; PMI: perioperative myocardial infarction; Af: atrial fibrillation; TIA: transient ischemic attack.

comparison to only one patient (0.2%) in the low-risk group (p = 0.002). Transient ischaemic attacks (TIA) were observed in 2.6% of patients in the high-risk group and 1.2% of those in the low-risk group (p = 0.30).

Delayed stroke occurred between the day of surgery and postoperative day 18 (mean postoperative day 8.8) as shown in Table 3. One delayed stroke occurred after postoperative coronary angiography, and one was due to hypotension caused by a drug allergy. The remaining six delayed strokes were caused by thrombo-embolism, and five of these occurred distal to the high-grade cerebrovascular stenosis. According to the univariate analysis, designation in the high-risk group was significantly associated with the occurrence of delayed stroke (p = 0.011) (Table 4). However, there was no significant association between age, male gender, preoperative/postoperative renal failure, diabetes mellitus, preoperative left ventricular ejection fraction, low cardiac output syndrome, perioperative myocardial infarction, episode of postoperative atrial fibrillation, postoperative coronary angiography and occurrence of delayed stroke.

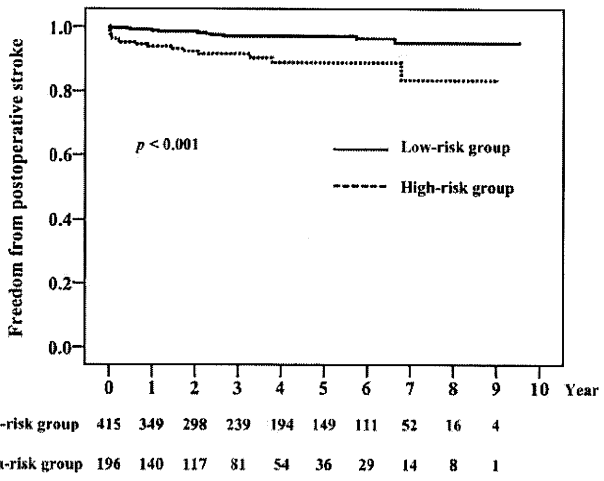

Fig. 2. Freedom from postoperative stroke.

Fig. 2 shows the relationship between the probability of remaining free from stroke and the amount of time after off-pump CABG in the two groups. The probability in the high-risk group decreased rapidly during the very early postoperative period, and this was followed by a more gradual decline over the next several years. The person-time incidence rate of stroke (stroke rate) in the high-risk group was much higher within 1 month (3.57) after CABG than that at later than 1 month (0.14) after a mean follow-up of 2.3 years (Table 5). A similar reduction in the stroke rate was also observed in the low-risk group, although it was less remarkable.

Table 3
Details of delayed stroke after off-pump CABG.

	Risk group	CVD (stenosis > 70%)	Episode of Af	Postop date of presentation	Area of infarct	Aetiology
Case 1	High	Bilateral CA	No	0 POD	Left hemisphere	Hypoperfusion
Case 2	High	Bilateral CA	Yes	8 POD	Left MCA	Thrombo-embolism
Case 3	High	Right CA	No	3 POD	Right hemisphere multiple	Thrombo-embolism
Case 4	High	Right CA	Yes	17 POD	Right thalamus	Embolism?
Case 5	High	Bilateral CA	Yes	10 POD	Left MCA	Thrombo-embolism
Case 6	High	Right CA	No	9 POD	Right MCA	Thrombo-embolism
Case 7	High	Bilateral ICA	No	18 POD	Right pons	Thrombo-embolism
Case 8	Low	No	Yes	5 POD	Left MCA	Thrombo-embolism

CVD: cerebrovascular disease; CA: carotid artery; ICA: intracranial artery; Af: atrial fibrillation; POD: postoperative day; MCA: middle cerebral artery.

Table 4
Univariate analysis of delayed stroke.

Variables	Delayed stroke (+) (n = 8)	Delayed stroke (−) (n = 603)	Odds ratio	95% CI	p value
High-risk group	87.5%	31.3%	15.33	1.87–125.51	0.011
Age (year)	68.8 ± 5.4	67.6 ± 9.0	1.02	0.94–1.10	0.71
Male gender	75.0%	78.9%	0.80	0.16–4.01	0.79
Preop renal failure	12.5%	14.5%	0.84	0.10-6.94	0.88
Diabetes	37.5%	46.5%	0.69	0.16–2.91	0.61
Preop LVEF (%)	70.4 ± 10.8	61.5 ± 14.6	1.05	0.99–1.11	0.090
LOS	12.5%	4.5%	3.04	0.36–25.62	0.31
PMI	12.5%	3.5%	3.94	0.46–33.48	0.21
Episode of postop Af	50.0%	26.0%	2.84	0.70–11.51	0.14
Postop angiography	62.5%	46.8%	0.53	0.13–2.23	0.38
Postop renal failure	25.0%	24.6%	1.02	0.20–5.11	0.98

CI: confidence interval; LVEF: left ventricular ejection fraction; LOS: low cardiac output syndrome; PMI: perioperative myocardial infarction; Af: atrial fibrillation.

Table 5
Stroke rate after off-pump CABG.

	Stroke rate <1 month	Stroke rate ≥1 month
High-risk group	3.75 (7/196)	0.14 (10/189)
Low-risk group	0.24 (1/415)	0.05 (10/414)

Stroke rate (r: incidence per 100 person-months) after off-pump CABG. $r = (N/D) \times 100$, where N is the number of strokes occurring during the observation period and D is person-time units (months).

4. Discussion

Atherosclerosis is a systemic disorder occurring throughout the vascular tree. Therefore, patients undergoing CABG are likely to develop severe atherosclerosis in the carotid/cranial arteries. The presence of significant cerebrovascular disease is believed to increase the risk of stroke after CABG.

Perioperative strokes associated with cerebrovascular disease can be divided into two principal aetiological mechanisms: hypoperfusion and thrombo-embolism. Hypoperfusion strokes arise from haemodynamic compromise distal to the carotid/cranial artery stenosis, and have been associated with the patients' capacity for cerebral autoregulation, which may be impaired by cardiopulmonary bypass [8]. Thrombo-embolic strokes are caused by thrombus formation at the site of the ulcerated atherosclerotic plaque on the carotid/cranial arteries [9].

Recent studies have shown that the use of the off-pump technique combined with minimal manipulation of the aorta can reduce the incidence of intra-operative stroke to almost zero [10–12]. These reports are in agreement with the findings of our study and, furthermore, there were no cases of intra-operative stroke after off-pump CABG even in patients with significant cerebrovascular disease (high-risk group). This result suggests that avoidance of cardiopulmonary bypass may preserve the capacity of cerebral autoregulation and, as a result, reduce the incidence of stroke associated with intra-operative hypoperfusion.

Eight patients in our study (1.3%) developed delayed stroke after off-pump CABG. Currently, the aetiological mechanism of delayed stroke is still unclear; atrial fibrillation and low ventricular ejection fraction have been suggested to contribute to its occurrence [4,12]. In our study, the presence of significant cerebrovascular disease (high-risk group) seemed to be a risk factor for delayed stroke (Table 4). However, there was no significant association between preoperative low left ventricular ejection fraction, episode of postoperative atrial fibrillation and occurrence of delayed stroke. Most of these infarctions occurred distal to the significant stenosis, and thrombo-embolism was the predominant aetiology.

Another important aspect of delayed stroke is that the incidence rates are not constant over time. Peel et al. reported that the incidence of delayed stroke increased rapidly after the day of off-pump CABG, reached a peak on postoperative day 4, and then decreased exponentially [13]. In our study, the incidence rate of stroke (stroke rate) in the high-risk group was much higher within 1 month (3.57) of off-pump CABG than that beyond 1 month (0.14) (Table 5).

One possible explanation for these phenomena is the increase in coagulability during the early postoperative period. According to a study by Parolari et al., activation of the coagulation–fibrinolytic system and endothelial cell damage increased at 4 and 8 postoperative days, returning to baseline levels 30 days after off-pump CABG [14]. Platelet activation has also been reported to gradually decrease until day 30, with a sudden increase in aggregation on day 2 [15]. Furthermore, the inhibition of platelet aggregation by aspirin seems to be compromised within a few days after off-pump CABG [16]. In our study, the predominant aetiology of delayed stroke was thrombo-embolism rather than hypoperfusion. Presumably, an increase in coagulability may accelerate the formation of thrombi at atherosclerotic lesions in carotid/cranial arteries. Therefore, high-risk patients may require aggressive anticoagulation/anti-platelet therapy for at least 30 days after off-pump CABG.

Our results raise the question whether patients in the high-risk group require either synchronous or staged carotid revascularisation plus off-pump CABG to prevent delayed stroke. According to a systematic review of patients undergoing staged/synchronous carotid endarterectomy and CABG, the incidence of stroke was around 4%, regardless of the timing of the procedure [17]. Guzman et al. reported that 6.1% of patients developed stroke from the time of prophylactic carotid stenting to 30 days after the CABG procedure [18]. Delayed strokes are usually associated with a better neurologic prognosis than intra-operative strokes [5]. In our study, seven patients (3.6%) in the high-risk group developed delayed stroke, and five of them recovered fully. Patients in the high-risk group were neurologically asymptomatic before surgery, and some of them had significant stenosis in the intracranial arteries rather than in the carotid arteries. Therefore, further investigation is required to elucidate, which patient in the high-risk group will benefit from the prophylactic carotid procedures.

Several limitations of this study needed to be addressed. This study was a retrospective non-randomised observational study. The number of study patients was relatively small ($n = 611$), and only eight delayed strokes were observed. This does not allow multivariate analysis to evaluate the independent effect of variables on the occurrence of delayed stroke. Imaging modalities (MRI/MRA, CT, angiography and ultrasonography) could make a diagnosis of thrombo-embolic stroke, and most of the delayed strokes occurred distal to the significant carotid/cranial artery stenosis. Although the thrombus was potentially derived from the heart, echocardiography could not reveal an intracardiac thrombus at the time of delayed strokes. We also did not investigate the haematologic variables of patients undergoing off-pump CABG. Therefore, further assessment would be required to confirm our hypothesis.

In conclusion, no intra-operative stroke was observed after off-pump CABG even in patients with significant cerebrovascular disease. However, these patients were likely to develop delayed stroke within 30 days of surgery.

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