

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,

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.

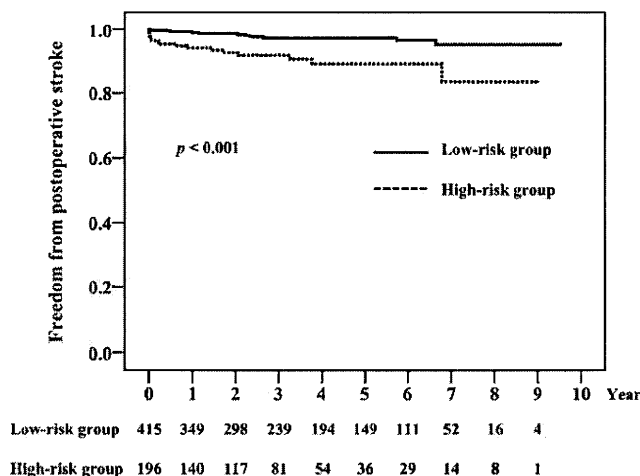


Fig. 2. Freedom from postoperative stroke.

episode of postoperative atrial fibrillation, postoperative coronary angiography and occurrence of delayed 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 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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