Optimal timing of preoperative aspirin cessation in coronary artery bypass grafting patients

（冠動脈バイパス術患者における術前アスピリン投与中止時期の検討）

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ABSTRACT

Objective

The timing of preoperative discontinuation of aspirin for patients undergoing coronary artery bypass grafting (CABG) in clinical practice seems to often differ from the current guidelines. We evaluated the effect of timing of aspirin cessation on morbidity and early and late mortality.

Methods

The timing of aspirin cessation for patients who underwent isolated coronary artery bypass grafting (CABG) was analysed using a prospectively collected data obtained from the Cardiac Surgery Database of the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) between 2001, and 2012. The patients were divided into 3 groups; continued to the day of surgery or stopped within 2 days prior to surgery (late use), stopped between 3 to 7 days prior to surgery (late discontinuation), and stopped more than 7 days prior to surgery (early discontinuation).

Results

16,988 patients who received aspirin prior to surgery underwent isolated CABG. There were 6,814 patients in the late use group, 3,634 in the late discontinuation group, and 6,540 in the early discontinuation group. Compared to the early discontinuation and late discontinuation group, the early drain output, and transfusion requirements were significantly higher in the late use group. Reoperation for bleeding was associated with late use. There was no significant difference in the 30-day and in hospital mortality.

Conclusions

Among patients undergoing elective isolated CABG, the timing of aspirin cessation was not associated with increased early mortality, but resulted in increased bleeding and transfusion requirement. The late use of preoperative aspirin still remains controversial.

INTRODUCTION

The administration of Aspirin early after coronary artery bypass grafting (CABG) has been shown to improve survival and graft patency, and reduce ischemic complications [1]. Guideline from The Society of Thoracic Surgeons (STS) [2] suggests that aspirin be discontinued in patients without acute coronary syndrome 3 to 5 days before surgery. On the other hand, the guideline from the American College of Cardiology/American Heart Association (ACC/AHA) [3] recommends aspirin to be administered preoperatively for CABG patients. Interestingly, the previous ACC/AHA guideline in 2004 suggested that aspirin be discontinued in patients without acute coronary syndrome undergoing CABG 7 to 10 days before surgery [4]. The management of perioperative aspirin dosing varies among surgeons and medical institutions especially when it comes to preoperative management. Backgrounds for stopping aspirin include the potential for increased bleeding and transfusion requirements during and after surgery [5,6], and a meta-analysis showed that preoperative aspirin increases postoperative bleeding, transfusion requirements, and chest reexploration for bleeding, while having no significant effect on MI or death [7]. However, these studies tend to be outdated, and recent studies are starting to show a shift in paradigm. Jacob et al. has reported that patients who had aspirin continued within 5 days of surgery (late use) received more intraoperative and postoperative transfusion, but a similar number of reoperations for bleeding compared with those who had their aspirin discontinued 6 or more days prior to surgery (early discontinuation) in patients undergoing CABG [8]. In patients undergoing CABG and valve surgery, they have reported that the late use group patients received more postoperative transfusions and tended to have increased reoperation for bleeding rate than early discontinuation group patients, but no difference in major adverse cardiac events [9]. We studied the effect of aspirin continuation prior to CABG on short and long term mortality.

METHODS

We analysed prospectively collected data obtained from the Cardiac Surgery Database of the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS). The data collection and its audit methods were discussed previously [10]. Data from this database has been approved for use in research by the institutional review board with patient consent waived. Long term mortality data were obtained from the Australian National Death Index which records all deaths within Australia. From June 2001 to December 2012, information on preoperative use of aspirin and other antiplatelet agents were prospectively collected in 17,218 patients undergoing non-emergent isolated CABG. The standard information collected was the timing of cessation and the agent used. The timing of aspirin cessation was divided into 3 groups; continued to the day of surgery or stopped within 2 days prior to surgery (late use), stopped between 3 to 7 days prior to surgery (late discontinuation), and stopped more than 7 days prior to surgery (early discontinuation).

Exclusion criteria included off-pump CABG, patients on antiplatelet agents other than aspirin, patients younger than 18 years of age, previous cardiac operation defined as surgical or non-surgical including all forms of percutaneous angioplasty and thrombolytic therapy for cardiac indications. Patients with active infective endocarditis were also excluded from this study.

The primary end points were 30-day and in-hospital mortality, myocardial infarction, and stroke. ANZSCTS definitions of myocardial infarction and stroke were used. Perioperative myocardial infarction is diagnosed by finding at least two of the following criteria: enzyme level elevation, new wall motion abnormalities, and serial electrocardiogram (at least two) showing new Q waves. Enzyme level elevation requires either creatine kinase-MB > 30 or troponin > 20 micrograms/L. Postoperative stroke is defined as a central neurologic deficit persisting for > 72 hours.

The secondary end points were reexploration for bleeding, drain output for the first 4 hours after the operation, total red blood cell (RBC) transfusion, platelet transfusion, and coronary reintervention.

Statistical methods

All analyses were performed with IBM SPSS statistical software. Continuous variables are reported as mean ± standard deviations and categorical variables are reported as percentages unless otherwise stated. Serum creatinine is in mmol and cross clamp and perfusion time in minutes. Student’s t test and one-way ANOVA tests were used in univariate analysis of continuous variables. Categorical data was analysed using the Pearson’s chi-square test.

The Cox proportional hazards regression method was used in multivariate assessment of differences between groups. We adjusted for pre-operative factors. Pre-operative variables included age, sex, body mass index, smoking history, diabetes mellitus, peripheral vascular disease, pre-operative serum creatinine, hypertension (defined as a blood pressure reading exceeding 140/90 mmHg, a history of high blood pressure or need for anti-hypertensive therapy), cerebrovascular disease, left main coronary artery disease > 50%, and urgent surgery. Intra-operative factors included total cross clamp time, intra-operative anti-fibrinolytic use, number of distal anastomoses, use of the left internal mammary artery, right internal mammary artery or both and perfusion time. Relative Risks (RR) were estimated, along with their associated 95% confidence intervals (CI). Statistical significance was accepted at the 0.05 level.

Long term mortality was estimated using Kaplan-Meier survival analysis and differences between groups detected via the log – rank test. Survival is reported at 1, 3, 5, and 7 years after surgery.

RESULTS

Between June 2001 and December 2012, 16,993 patients taking aspirin preoperatively underwent non-emergent isolated CABG. Of those, 6,814 patients (40.1%) continued aspirin use up to the surgery or ceased within 2 days of surgery (late use), 3,634 patients (21.4%) stopped their aspirin use between 3 to 7 days prior to surgery (late discontinuation), and 6,540 patients (38.5%) stopped their aspirin use more than 7 days prior to surgery (early discontinuation). The demographic, and procedural data are included in Table 1.

The patient characteristics were similar between the late use group, late discontinuation group, and early discontinuation group with patients on aspirin in regards to age, number of female, body mass index (BMI), smoking history, hypertension, diabetes, history of cerebrovascular disease (CVA), peripheral vascular disease, and serum Creatinine level. The rate of left main artery disease tended to be higher in the late use group (32.1% versus 23.6% versus 20.0%, respectively). When the urgency of surgery was compared, there were significantly more patients who underwent urgent surgery in the late use group than in the other two groups (48.8% versus 29.7% versus 17.8%).

The use of cardiopulmonary bypass (CPB), total bypass time, total cross clamp time, number of anastomoses, use of 1 or 2 internal mammary arteries, and intraoperative antifibrinolytic use were similar amongst the three groups.

When comparing the end points between the late use group and late discontinuation group, the drain output at 4 hours after surgery was significantly higher (283.15 ± 294.97 ml versus 243.04 ± 213.21 ml, $P<0.001$), and the units of red blood cells and platelets transfused were significantly higher in the late use group (2.89 ± 3.09 versus 2.45 ± 3.28, $P<0.001$; 1.63 ± 2.39 versus 1.66 ± 12.58, $P<0.001$, respectively) (Table 2). Though this resulted in increased rate of reoperation for bleeding (2.4% versus 2.1%, $P=0.001$) and return to theatre (5.0% versus 4.3%, $P<0.001$), there was no significant difference regarding the 30 day and in hospital mortality (1.4% versus 0.9%, $P=0.228$; 1.5% versus 1.1%, $P=0.454$, respectively).

Similar results were seen when the endpoints were compared between the early discontinuation group and late use group (Table 3). No significant difference was noted in regards to 30-day and in hospital mortality. The drain output at 4 hours after surgery was significantly higher (283.15 ± 294.97 ml versus 265.54 ± 286.82 ml, $P<0.001$), and the units of red blood cells and platelets transfused were significantly higher in the late use group (2.89 ± 3.09 versus 2.68 ± 3.58, $P<0.001$; 1.63 ± 2.39 versus 1.66 ± 12.58, $P<0.001$, respectively). The incidence of return to theatre and reoperation for bleeding was also higher (5.0% versus 4.1%, $P<0.001$; 2.4% versus 2.0%, $P<0.001$, respectively). Perioperative myocardial infarction and permanent stroke was more commonly seen in the late use group (0.6% versus 0.3%, $P=0.002$; 0.8% versus 0.6%, $P=0.016$, respectively).

When comparing the early discontinuation group and late discontinuation group, there was no significant difference in 30-day mortality or in-hospital mortality, but more incidences of transient and permanent stroke (0.3% versus 0.6%, *P*=0.031; 0.6% versus 0.8%, *P*=0.030, respectively) and perioperative MI (0.3% versus 0.8%, *P*=0.005) were seen in the late discontinuation group (Table 4). However, the late discontinuation group had less drain output (243.04 ± 213.21 ml versus 265.54 ± 286.82 ml, *P*=0.006).

On the other hand, the long term survival tended to be better at 5 and 7 years in the late use group compared to late discontinuation and early discontinuation group (94.1% versus 93.6% versus 93.3% at 5 years, 93.1% versus 92.0% versus 91.9% at 7 years), but there was no significant difference (Figure 1).

DISCUSSION

The current guideline from STS suggests discontinuation of aspirin 3 to 5 days prior to CABG [2]. ACC/AHA guideline has recently changed their recommendation from ceasing 7 to 10 days prior to CABG to administering preoperatively [3,4]. The recommendations are controversial, and in clinical practice, this is also the case. In our study, approximately 40% of the patients undergoing isolated CABG had continued aspirin until less than 2 days prior to surgery. The risk of bleeding intraoperatively and postoperatively leading to morbidity and mortality are the foci for discontinuation of aspirin prior to surgery. It has also been previously reported that perioperative red blood cell transfusion is associated with significantly reduced long-term survival in patients undergoing isolated CABG [11]. STS base the timing of aspirin cessation on platelet physiology. Because aspirin is an irreversible cyclooxygenase inhibitor, the life span of a platelet (approximately 7 to 10 days) is an important factor in deciding how many days are needed to wait for enough new platelets to be formed. Cessation of aspirin 5 days prior to surgery is suggested as it takes 3 to 5 days for half of the platelet pool to be regenerated, and this may be enough to normalize bleeding time and thromboxane B_2 levels.

The increased amount of postoperative bleeding and the need for red blood cells and platelets transfusion were similar to some of the previous literature [5,8,12]. In this study, the difference of drain output at 4 hours after surgery was approximately 40 to 60 ml. This was statistically significant, though may not seem clinically significant. However, the significant difference in transfusion requirements in the late use group does suggest clinical relevance.

Previous large retrospective studies showed no significant difference in the drain output postoperatively [13-15]. But Dacey et al. assigned the patients to preoperative aspirin group if the patients were exposed to aspirin within 7 days prior to surgery [13] and 5 days in the publication by Bybee et al [14]. These data may not represent the patients who were on aspirin until the operation. Dacey et al. compared in-hospital deaths with survivors to assess the factors associated with mortality by using case patient – control patient methodology [13]. This showed CABG patients using preoperative aspirin were less likely to experience in-hospital mortality in univariate and multivariate anaysis (odds ratio [OR] = 0.73, 95% confidence interval [0.54, 0.97], OR = 0.55, [0.31, 0.98], respectively). Aspirin use was defined by identification of ingestion within 7 days before the operation in this study, therefore, this does not represent the patients who were taking aspirin up to the day of surgery.

Increased drain output was seen in a different large retrospective study by Jacob et al. where the patients taking aspirin within 5 days prior to surgery was included in the late use group [8]. More recently, Deja et al. showed significant increase of bleeding in patients who were loaded with 300 mg of aspirin the night before surgery in a randomized trial [12]. In these studies, there was no significant difference in mortality or number of reoperations for bleeding. In our study, the late use group were patients who were on chronic aspirin up to less than 2 days prior to surgery.

As early postoperative aspirin administration is known to improve graft patency [16] and reduce ischemic complications [1], we did not expect to see more perioperative MI in the late use group. This may be due to the decreased haemoglobin or compromised haemodynamic state postoperatively due to the increase in bleeding. This also may be a product of the procoagulant effects of blood products or additional protamine given to treat bleeding. Recommencing of aspirin may have been delayed in patients with bleeding complications postoperatively owing to this outcome.

From our results, cessation of aspirin prior to CABG seems to be a reasonable decision in elective CABG patients. Moreover, ceasing 7 days prior to surgery rather than 3 to 7 days prior had reduced risk of transient and permanent stroke, and perioperative myocardial infarction, which suggests early discontinuation may be the preferred choice.

The tendency for improved long term survival in the late use group is the only supporting result for continuation as this is the key aim when continuing aspirin up to the day of surgery. This could be a late effect of improved graft patency with late use of aspirin, though this is only a speculation as routine postoperative angiography was not performed. Deja et al. showed a tendency to decrease the chance of a major cardiac event and decreased by 40% the long-term hazard of a coronary event developing [12].

The data used for this study is derived from a very large database compiled from multiple institutions, where the decision for aspirin use/cessation is surgeon/institution dependent and not regulated by protocol. Therefore, these results are likely to reflect real life practice where there is often high variability.

Surgeons need to take into consideration the preoperative status of each patient when deciding if aspirin needs to be discontinued. Is an increase in early mortality an acceptable price to pay for improved late outcome? It may well be, especially in young patients that are expected to live more than 10 years postoperatively. But in the current state where there is little to no evidence that there is improvement in long term outcome, we still need to be cautious in continuing aspirin prior to surgery.

Study Limitations

We were not able to obtain data regarding the dosage of the preoperative aspirin use or the timing of postoperative use of antiplatelets which may have had a significant impact on the postoperative outcomes. We are also unaware of the incident rate of ischemic events prior to surgery in those who had their aspirin ceased.

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Table 1: Patient demographics and intraoperative data

Characteristic	Isolated CABG – Aspirin (N=16993)		
	<2 Days (N=6814)	3-7 Days (N=3634)	>7 Days (N=6540)
Age – yr (Mean ± SD)	66.36 ± 10.50	66.44 ± 10.07	66.41 ± 10.10
Sex – female no. (%)	1419 (20.8)	751 (20.7)	1318 (20.2)
Body Mass Index (Mean ± SD)	28.78 ± 7.72	28.89 ± 7.53	29.23 ± 11.78
Smoking History (Current Smokers) n, (%)	4452 (65.4) 1206 (27.1)	2376 (64.4) 482 (19.6)	4208 (64.4) 878 (20.5)
Hypertension n, (%)	5429 (79.7)	2971 (81.8)	5284 (80.8)
Cerebrovascular Disease n, (%)	684 (10.0)	411 (11.3)	700 (10.7)
Left Main Artery Stenosis >50% n, (%)	2186 (32.1)	857 (23.6)	1310 (20.0)
Diabetes n, (%)	2412 (35.4)	1306 (35.9)	2317 (35.4)
Peripheral Vascular Disease n, (%)	759 (11.1)	434 (11.9)	719 (11.0)
Preoperative Serum Creatinine (mmol) - Female (Mean ± SD) (Male)	1.16 ± 0.39 (1.07 ± 0.40)	1.15 ± 0.41 (1.06 ± 0.41)	1.16 ± 0.40 (1.08 ± 0.40)
Urgent Surgery n, (%)	3324 (48.8)	1078 (29.7)	1164 (17.8)
Perfusion Time (mins) mean ± SD	93.81 ± 33.09	93.36 ± 33.52	90.85 ± 33.98
Cross Clamp Time (mins) mean ± SD	68.30 ± 29.57	66.37 ± 26.57	65.40 ± 31.87
Total Distal Anastomoses mean ± SD	3.35 ± 1.00	3.35 ± (1.00)	3.26 ± 1.01
LIMA n, (%)	6537 (99)	3485 (99.3)	6205 (99.3)

RIMA n, (%)	683 (10.4)	309 (8.8)	482 (7.7)
BIMA n, (%)	666 (9.8)	298 (8.2)	457 (7.0)
Intraoperative Antifibrinolytic Use n, (%)	3887 (79.6)	1671 (75.2)	2957 (75.1)

Table 2: Late use versus late discontinuation outcomes

Aspirin CABG	<2 Days (N=6814)	3-7 Days (N=3634)	P-value	RR
30 Day Mortality n, (%)	94 (1.4)	34 (0.9)	0.381	0.800
In Hospital Mortality n, (%)	105 (1.5)	39 (1.1)	0.615	0.891
Drain Losses at 4 hours n, (%)	283.15 ± 294.97	243.04 ± 213.21	<0.001	0.698
Units of PRBC Transfused n, (%)	2.89 ± 3.09	2.45 ± 3.28	<0.001	0.622
Units of Platelets Transfused n, (%)	1.63 ± 2.39	0.9 ± 2.12	<0.001	0.484
Reoperation for Bleeding n, (%)	164 (2.4)	76 (2.1)	<0.001	0.524
Return to Theatre (RTT) n, (%)	338 (5.0)	155 (4.3)	<0.001	0.593
Reoperation for Graft Occlusion n, (%)	5 (0.1)	1 (0.0)	0.539	0.509
Permanent Stroke n, (%)	54 (0.8)	29 (0.8)	0.876	0.957
Transient Stroke n, (%)	22 (0.3)	21 (0.6)	0.363	1.421
Perioperative Myocardial Infarction n, (%)	42 (0.6)	28 (0.8)	0.755	0.903

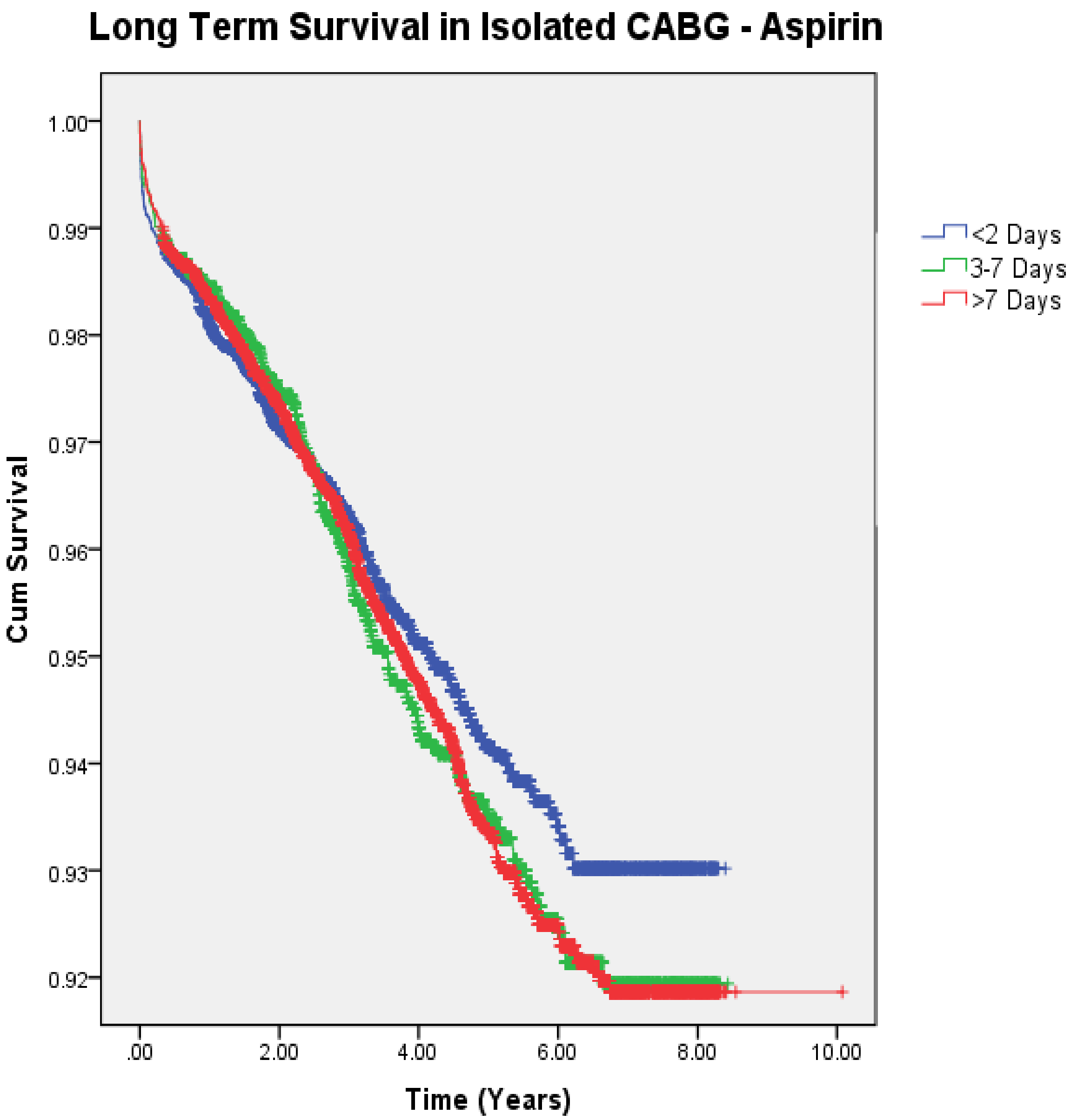
Table 3: Early discontinuation versus late use outcomes

Aspirin CABG	>7 Days (N=6540)	<2 Days (N=6814)	P-value	RR
30 Day Mortality n, (%)	58 (0.9)	94 (1.4)	0.174	1.372
In Hospital Mortality n, (%)	78 (1.2)	105 (1.5)	0.316	1.232
Drain Losses at 4 hours n, (%)	265. 54 ± 286.82	283.15 ± 294.97	<0.001	1.614
Units of PRBC Transfused n, (%)	2.68 ± 3.58	2.89 ± 3.09	<0.001	1.595
Units of Platelets Transfused n, (%)	1.66 ± 12.58	1.63 ± 2.39	<0.001	1.992
Reoperation for Bleeding n, (%)	130 (2.0)	164 (2.4)	<0.001	2.069
Return to Theatre (RTT) n, (%)	266 (4.1)	338 (5.0)	<0.001	1.876
Reoperation for Graft Occlusion n, (%)	4 (0.1)	5 (0.1)	0.372	0.538
Permanent Stroke n, (%)	40 (0.6)	54 (0.8)	0.016	2.027
Transient Stroke n, (%)	18 (0.3)	22 (0.3)	0.213	1.707
Perioperative Myocardial Infarction n, (%)	22 (0.3)	42 (0.6)	0.002	3.19

Table 4: Early discontinuation versus late discontinuation outcomes

Aspirin CABG	>7 Days (N=6540)	3-7 Days (N=3634)	P-value	RR
30 Day Mortality n, (%)	58 (0.9)	34 (0.9)	0.773	1.098
In Hospital Mortality n, (%)	78 (1.2)	39 (1.1)	0.699	1.098
Drain Losses at 4 hours n, (%)	265. 54 ± 286.82	243.04 ± 213.21	<0.001	1.126
Units of PRBC Transfused n, (%)	2.68 ± 3.58	2.45 ± 3.28	0.870	0.993
Units of Platelets Transfused n, (%)	1.66 ± 12.58	0.9 ± 2.12	0.626	0.964
Reoperation for Bleeding n, (%)	130 (2.0)	76 (2.1)	0.658	1.085
Return to Theatre (RTT) n, (%)	266 (4.1)	155 (4.3)	0.403	1.112
Reoperation for Graft Occlusion n, (%)	4 (0.1)	1 (0.0)	0.25	0.274
Permanent Stroke n, (%)	40 (0.6)	29 (0.8)	0.03	1.94
Transient Stroke n, (%)	18 (0.3)	21 (0.6)	0.031	2.425
Perioperative Myocardial Infarction n, (%)	22 (0.3)	28 (0.8)	0.005	2.882

Figure 1



Patient Group	Number	1 Year	3 Year	5 Year	7 Year
<2 Days	6814	6690 (124)	6607 (207)	6556 (258)	6545 (269)
3-7 Days	3634	3578 (56)	3507 (127)	3465 (169)	3452 (182)
>7 Days	6545	6439 (106)	6328 (217)	6241 (304)	6216 (329)

The Journal of Thoracic and Cardiovascular Surgery

平成 26 年 12 月　投稿中