Ann Thorac Cardiovasc Surg 2022; 28: 63–71
Online January 17, 2022
doi: 10.5761/atcs.oa.21-00236

Original Article

Therapeutic-Dose Warfarin (International Normalized Ratio >1.6) Plus Aspirin Improved Long-Term Patency of Saphenous Vein Graft without Bleeding Complication

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Purpose: Saphenous vein graft (SVG) is the most commonly used conduits in coronary artery bypass grafting (CABG), but the disadvantage of SVG is its tendency for progressive failure. We hypothesized that therapeutic-dose warfarin (international normalized ratio [INR] >1.6) plus aspirin improve SVG patency. This study aimed to evaluate the factors contributing to SVG patency.
Methods: Since 2010–2020, 199 patients who underwent isolated CABG using SVG were divided into two groups according to their INR values in the first year: group T (INR >1.6) and group L (INR <1.6).
Results: Group T had 162 SVGs (105 patients) and group L had 151 SVGs (94 patients). The 1-, 4-, and 7-year SVG patency rates were higher in group T than in group L (99%, 96%, and 92% vs. 93%, 86%, and 79%, respectively; $p = 0.00378$). The 1-, 4-, and 7-year freedom from repeat-revascularization was higher in group T than in group L (100%, 100%, and 99% vs. 98%, 95%, and 87%, respectively; $p = 0.0264$). Multivariate analysis showed that therapeutic-dose warfarin ($p = 0.00204$) and target vessel diameter ($p < 0.0001$) were independent risk factors of SVG occlusion.
Conclusion: Therapeutic-dose warfarin (INR >1.6) plus aspirin after CABG improved the long-term patency of SVG and decreased repeat-revascularization rate.

Keywords: warfarin, aspirin, SVG, CABG, patency

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Introduction

Internal thoracic artery (ITA) grafting is the gold standard for left anterior descending (LAD) coronary artery revascularization; however, the best conduit to use for other arterial branches is still controversial. In current practice, approximately 80% of all bypass conduits are saphenous vein grafts (SVGs) because of its availability and ease of use compared to arterial conduits.[1)] The major disadvantage of the SVG is its tendency for progressive failure during the follow-up period. In previous studies, the possibilities of SVG patency improvement with harvest techniques and external devices and their

administration are reported, but this information is not yet sufficient.[2–5)]

SVG occlusion is a multifactorial event. Initially, it occurs due to mechanical and technical factors resulting in endothelial injury and activation of subsequent thrombosis.[2–4)] Aspirin should be continued indefinitely to reduce graft occlusion (Class I).[5)] On the other hand, it is recommended that warfarin should not be routinely prescribed after coronary artery bypass grafting (CABG) for graft patency, except when patients have other indications for long-term antithrombotic therapy according to the guidelines for secondary prevention after CABG (Class III).[5)] In the Post-CABG trial,[6)] which has been adopted in some guidelines for coronary artery disease, it was reported that there were no significant differences in angiographic outcomes between the low-dose warfarin and placebo groups. In the study, the mean international normalized ratio (INR) was 1.4 in the low-dose warfarin group and 1.05 in the placebo group. We speculated that the mean INR of 1.4 is not sufficient to evaluate the effect of warfarin, especially for preventing SVG occlusion. There are other studies in which it was reported that administration of therapeutic-dose warfarin (mean INR was between 1.5 and 2.0) along with aspirin was associated with a decreased rate of repeat-revascularization and improved long-term patency.[7–9)] Based on previous reports on valvular heart disease[10)] and atrial fibrillation,[11)] we hypothesized that the optimal INR for the therapeutic-dose of warfarin to prevent thrombus formation is greater than 1.6. The aim of this study was to evaluate the factors for SVG patency, especially warfarin administration.

Materials and Methods

Study population

We performed a retrospective cohort study of consecutive patients who underwent isolated CABG at Musashino Red Cross Hospital between April 2010 and June 2020. Of these patients, patients who did not receive SVG, died in-hospital, were not evaluated with angiographic examination due to their reduced kidney function, or had a history of warfarin allergy were excluded. Patients with SVGs who were occluded at discharge or SVG harvested with the no-touch technique were also excluded. The study protocol was approved by the institutional review board of Musashino Red Cross Hospital, Tokyo, Japan (No. 3046). The requirement for obtaining informed patient consent was waived by the institutional review board because of the retrospective nature of the current study, and this work was carried out in accordance with the principles embodied in the Declaration of Helsinki and its revisions.

Study end points

The primary outcomes of interest were all-cause mortality, SVG patency, and repeat-revascularization. The secondary outcomes included bleeding complications requiring hospital admission and verification of the risk factors of SVG occlusion. Repeat-revascularization was defined as percutaneous coronary intervention (PCI) or CABG.

SVG harvest technique

Dissection of SVG was performed by using the standard technique through classical open incisions, harvest of the saphenous vein in the thigh, followed by a continuous suture of the incision. The perivascular tissue was incised, and side branches were ligated with 5-0 silk or titanium clips. SVG was gently distended after having been removed with saline and heparin using a syringe, and layered closure of the wound was performed using an absorbable suture material.

Surgical aspect

All procedures were performed via a median sternotomy incision. ITA and gastroepiploic artery were harvested using a harmonic scalpel by a standard technique. Patients received intravenous heparin to maintain the activated clotting time of more than 300 seconds, from the termination of conduit harvest to the completion of all anastomoses. In almost all patients, the LAD was revascularized first with ITA before SVG anastomoses. The ascending aorta was assessed using epiaortic echocardiography, then the proximal anastomosis of SVG was constructed using proximal anastomotic devices and continuous 7-0 polypropylene sutures. The distal anastomosis of SVG was constructed with continuous 7-0 polypropylene sutures. Each time after anastomosis, the graft flow was evaluated using transit-time flow meter and revised if there were any abnormal findings.

Medication

If the patient took aspirin preoperatively, aspirin was discontinued on the day of operation. Intravenous heparin was started 6 hours after CABG to maintain the activated clotting time between 150 and 220 seconds, and aspirin and warfarin were started after the patients had resumed oral intake. The initial dose of warfarin was 2 mg, and the daily dose of warfarin was increased until an

INR value of 1.6 or higher. Intravenous heparin was discontinued when the INR value reached to 1.6. Aspirin and warfarin were administered indefinitely. If the preoperative low-density lipoprotein cholesterol was greater than 100 mg/dL, statin was started preoperatively. As a result, most patients received statins prior to CABG.

Grouping based on warfarin administration

After the patients were discharged from our hospital, we recorded their INR values every month for the first 6 months and every few months thereafter. In this study, an INR value defined as a therapeutic dose of warfarin was more than 1.6. We divided the patients into the following two groups according to the time in therapeutic range (TTR) for the first year after CABG: group T (INR >1.6) and group L (INR <1.6). Patients with an optimal INR above 70% of TTR were considered to be under good control and were referred to as the therapeutic-dose group (group T), while the remaining patients were categorized as the low-dose group (group L).

Angiographic evaluation

SVG was evaluated with multi-slice coronary computed tomographic angiography (CCTA) or coronary angiography (CAG) before discharge. Target vessel diameter was measured at the distal side of the SVG anastomosis. In patients with a normal renal function, follow-up CCTA was performed every year postoperatively. In patients with an estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m^2, CCTA was performed after appropriate hydration. In patients with an eGFR <30 ml/min/1.73 m^2, myocardial adenosine stress thallium-201 scintigraphy was performed, instead of CCTA, in these patients, and they were excluded from follow-up in this study. In the event of new-onset angina, however, CCTA or CAG was performed immediately. The patency rate was graded according to the FitzGibbon classification,[12] which grades graft patency as A (widely patent), B (flow limited), or O (occluded). For the purpose of our analysis, grades A and B were considered patent, and grade O was occluded.

Data analysis

Data are expressed as median and inter-quartile range for continuous variables and as numbers with percentages for categorical variables. Statistical analyses of the clinical data were performed with Fisher's exact probability test, Pearson's correlation test, and Student's t-test. Patency rates were estimated using the Kaplan–Meier method, and intergroup comparison was performed using log-rank tests. Cox-regression analysis and the Cox proportional hazards model were used for graft occlusion risk factor analysis. Values of p <0.05 were considered statistically significant. The statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[13]

Results

According to the cardiac surgical database of Musashino Red Cross Hospital, where all patients who underwent cardiac surgery were prospectively registered, a total of 408 adult patients (aged 20 years or older) underwent isolated CABG from April 2010 to June 2020. Among them, SVGs were used in 301 patients. Patients who died in hospital (9 patients), were not evaluated with angiographic examination (25 patients) due to their reduced kidney function, or had a history of warfarin allergy (3 patients) were excluded. Those with SVGs who were occluded at discharge (6 patients) and harvested with the no-touch technique (59 patients) were also excluded. After exclusion of patients, a total of 313 SVGs (199 patients) were reviewed in this study. In groups T and L, 162 (105 patients) and 151 (94 patients) SVGs were evaluated, respectively. The preoperative patient characteristics and operative details are shown in **Table 1**, and details related to SVG are shown in **Table 2**. There was no significant difference in the data between the two groups.

Primary outcome

During a median follow-up of 54.7 months (interquartile range, 27.3–83.4 months), there were a total of 17 (16%) post-discharge deaths in group T and 9 (9.6%) in group L. There were no differences between the two groups in the overall survival (p = 0.141). From the SVG patency evaluation, 8 (4.9%) occluded SVGs were found in group T and 23 (15%) in group L (odds ratio, 0.295; 95% CI, 0.110–0.713; p = 0.00388). The SVG patency was higher in group T than in group L (1-, 4-, and 7-year values: 99%, 96%, and 92% in group T and 93%, 86%, and 79% in group L, respectively; hazard ratio, 0.305; 95% CI, 0.136–0.681; p = 0.00378) (**Fig. 1**). Repeat-revascularization was performed for 1 SVG (0.6%) in group T and 9 SVGs (6.0%) in group L (odds ratio, 0.0986; 95% CI, 0.00223–0.726; p = 0.00843). PCI was performed in all repeat-revascularization cases on a territory that revealed new onset myocardial ischemia due to

Table 1 Preoperative and operative details

Variables	Group T	Group L	*p*-value
Preoperative details			
Total number of patients	105	94	
Total number of SVGs	162	151	
Age (years)	73 (68–78)	74 (68–78)	0.684
Male	87 (83%)	75 (80%)	0.590
Body mass index (kg/m^2)	23.2 (21.3–25.5)	23.5 (20.8–25.4)	0.274
NYHA grade III or IV	15 (14%)	11 (11%)	0.676
Hypertension	95 (91%)	79 (84%)	0.202
Dyslipidemia	88 (84%)	76 (81%)	0.778
Diabetes mellitus: insulin-use	22 (21%)	21 (22%)	0.864
Chronic kidney disease: on hemodialysis	10 (9.5%)	19 (20%)	0.075
Chronic kidney disease: eGFR <50 (ml/minute/1.73 m^2)	29 (28%)	34 (36%)	0.358
Atrial fibrillation	3 (2.9%)	3 (3.2%)	0.668
Prior percutaneous coronary intervention	28 (27%)	23 (25%)	0.748
Prior cerebrovascular event	6 (5.7%)	10 (11%)	0.296
LVEF (%)	60.6 (51.5–69.9)	58.4 (47.6–70.3)	0.209
Operative details			
Off pump CABG	101 (96%)	89 (95%)	0.738
Number of distal anastomoses	5 (4–5)	5 (4–5)	0.561

Values are expressed as median and interquartile range (IQR) or number (%). SVG: saphenous vein graft; NYHA: New York Heart Association; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting

Table 2 SVG details

Variables	Group T	Group L	*p*-value
Total number of patients	105	94	
Total number of SVGs	162	151	
Target site of SVG			
Right coronary artery	74 (46%)	74 (49%)	0.349
Left circumflex	82 (51%)	67 (44%)	
Diagonal branch	6 (3.7%)	10 (6.6%)	
All graft			
Target vessel stenosis ≤75%	28 (17%)	30 (20%)	0.564
Target vessel diameter (mm)	1.7 (1.5–1.9)	1.7 (1.5–1.9)	0.858
SVG diameter (mm)	4.0 (3.3–4.5)	4.1 (3.5–4.7)	0.355
Size mismatch (diameter of SVG/target vessel)	2.3 (2.1–2.6)	2.4 (2.1–2.7)	0.238
Proximal anastomosed devise			
Heart string	95 (58%)	87 (58%)	0.064
Enclose	51 (32%)	36 (24%)	
Passport	16 (9.9%)	28 (19%)	
Proximal anastomosed site			
Ascending aorta	135 (89%)	141 (87%)	0.905
SVG (Y-composite)	27 (11%)	16 (13%)	
Graft design			
Individual	53 (33%)	56 (37%)	0.476
Sequential	109 (67%)	95 (63%)	

Values are expressed as median and interquartile range (IQR) or number (%). SVG: saphenous vein graft

SVG occlusion. The freedom from repeat-revascularization rate was higher in group T than in group L (1-, 4-, and 7-year values: 100%, 100%, and 99% in group T and 98%, 95%, and 87% in group L, respectively; hazard ratio, 0.0962; 95% CI, 0.0122–0.760; $p = 0.0264$) (**Fig. 1**).

Secondary outcomes

Bleeding complications resulting in admission were observed in 6 (5.7%) and 8 (8.5%) patients in groups T and L, respectively (odds ratio, 1.50; 95% CI, 0.437–5.48; $p = 0.581$). No patient died of bleeding complications; however, one patient in group L underwent a surgical intervention for a chronic subdural hematoma at 2 months after CABG. In the univariate analysis, therapeutic-dose warfarin ($p = 0.00378$), smaller target vessel diameter ($p < 0.0001$), and size mismatch (greater ratio of the diameter of SVG/target vessels) ($p < 0.0001$) were significant risk factors for SVG occlusion (**Table 3**).

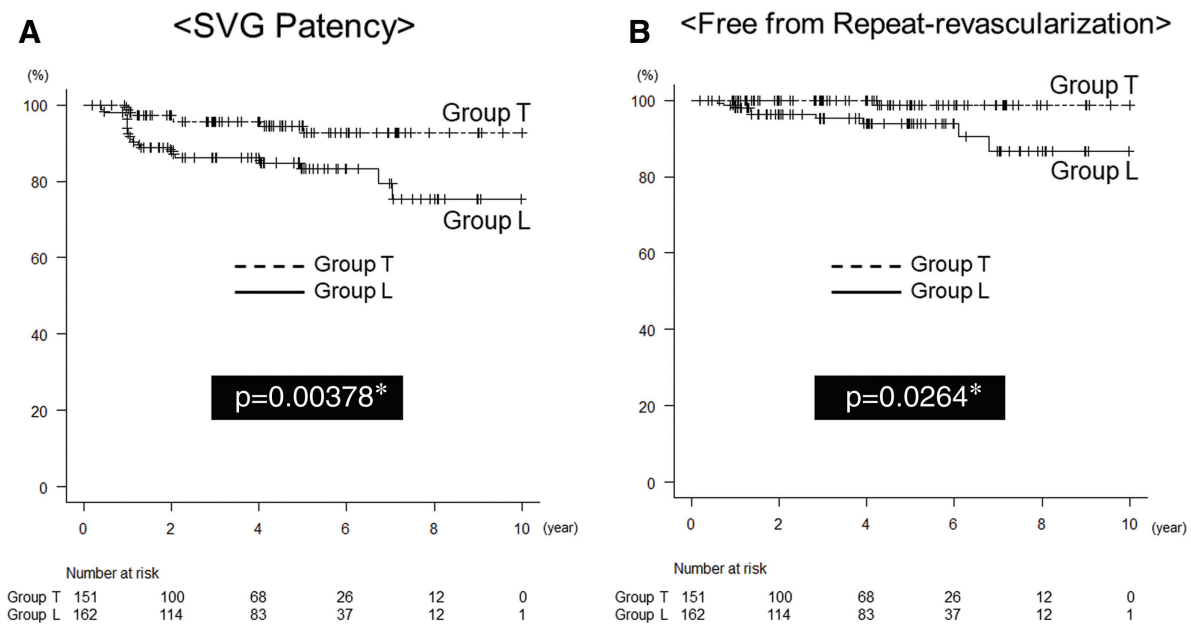

Fig. 1 Comparison of (**A**) SVG patency rates and (**B**) free from repeat-revascularization rates between Group T and Group L using log-rank tests. *p <0.05. SVG: saphenous vein graft

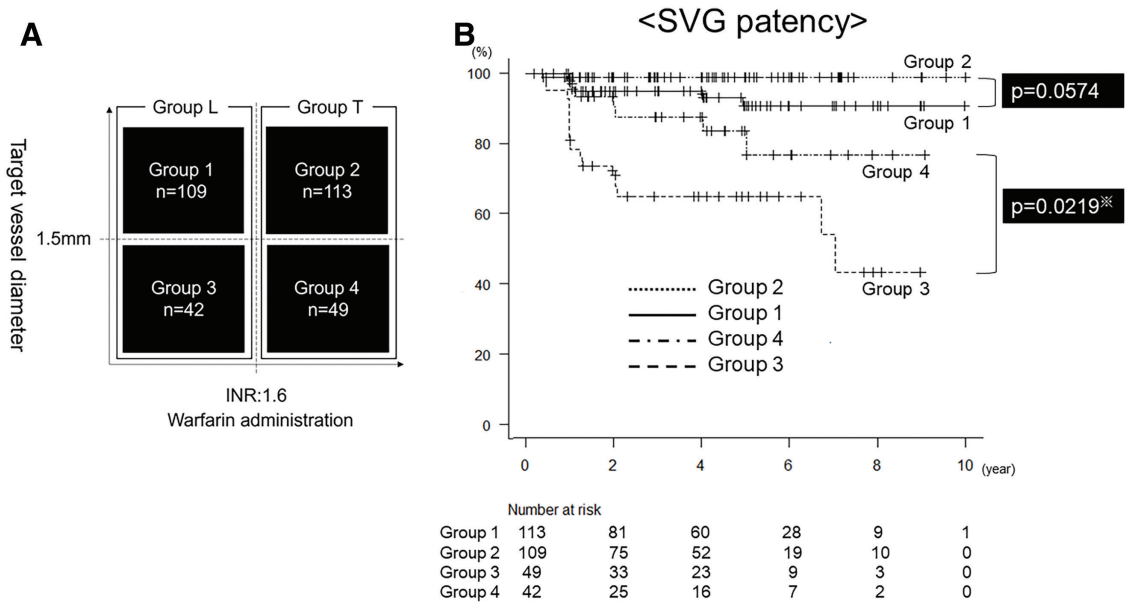

Fig. 2 (**A**) Groups 1 and 2 from groups L and T, respectively, comprised SVGs anastomosed to larger target vessel diameters (>1.5 mm). Groups 3 and 4 from groups L and T, respectively, included SVGs anastomosed to smaller target vessel diameters (<1.5 mm). (**B**) Comparison of SVG patency rates among four groups using log-rank tests. *p <0.05. SVG: saphenous vein graft; INR: international normalized ratio

Multivariate analysis showed that therapeutic-dose warfarin (hazard ratio, 0.279; 95% CI, 0.124–0.628; p = 0.00204) and target vessel diameter (hazard ratio, 0.0519; 95% CI, 0.0144–0.187; p <0.0001) were independent factors of SVG occlusion (**Table 3**). The receiver operating characteristic curve for the target vessel diameter was calculated. The cut-off value of the target vessel diameter was 1.5 mm, calculated from the point of maximal specificity (75.9%) and sensitivity (74.2%), and the area under the curve was 0.802. Groups 1 and 2 from groups L and T, respectively, comprised SVGs anastomosed to larger target vessel diameters (>1.5 mm). In

Table 3 Risk factor analysis for SVG occlusion

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (CI)	*p*-value	Hazard ratio (CI)	*p*-value
Age	0.971 (0.925–1.02)	0.234		
Male	1.48 (0.518–4.24)	0.463		
Diabetes mellitus: insulin-use	1.09 (0.445–2.65)	0.857		
Chronic kidney disease: on hemodialysis	1.94 (0.832–4.51)	0.125		
Left ventricular ejection fraction (%)	0.989 (0.964–1.01)	0.365		
Stenosis grade <75%	1.02 (0.418–2.49)	0.989		
Statin	1.30 (0.453–3.71)	0.660		
DAPT + warfarin	Out of range	0.997		
Therapeutic-dose warfarin: Group T (INR >1.6)	0.305 (0.136–0.681)	0.00378*	0.279 (0.124–0.628)	0.00204*
Target site of SVG				
Right coronary artery		Reference		
Left circumflex	1.37 (0.650–2.91)	0.406		
Diagonal branch	2.57 (0.725–9.14)	0.144		
Proximal anastomosed device				
Enclose II		Reference		
Heartstring III	0.595 (0.239–1.48)	0.264		
Passport	0.995 (0.318–2.71)	0.892		
TTFM data				
Pulsatility index	0.972 (0.835–1.13)	0.719		
Mean graft flow (ml/min)	1.00 (0.993–1.01)	0.577		
Diastolic filling (%)	1.02 (0.985–1.05)	0.280		
Target vessel diameter (mm)	0.0382 (0.0144–0.101)	<0.0001*	0.0519 (0.0144–0.187)	<0.0001*
SVG diameter (mm)	0.695 (0.468–1.03)	0.0707		
Size mismatch (diameter ratio of SVG/target vessel)	2.95 (2.00–4.33)	<0.0001*	1.29 (0.774–2.16)	0.327

*p <0.05.Values are expressed as median and interquartile range (IQR) or number (%). SVG: saphenous vein graft; DAPT: dual antiplatelet therapy; TTFM: transit-time flow measurement

groups 1 and 2, a high SVG patency rate was observed and there was no significant difference between these two groups (**Fig. 2**). Groups 3 and 4 from groups L and T, respectively, included SVGs anastomosed to smaller target vessel diameters (<1.5 mm). SVG patency was higher in group 4 than in group 3 (hazard ratio, 0.354; 95% CI, 0.145–0.860; $p = 0.0219$) (**Fig. 2**), and administration of therapeutic-dose warfarin (INR >1.6) plus aspirin was more effective for SVG patency anastomosed to smaller diameter target vessels.

Discussion

We hypothesized that therapeutic-dose warfarin (INR >1.6) plus aspirin may be effective in preventing thrombus formation during the early postoperative period, improving long-term SVG patency, and decreasing the repeat-revascularization rate especially for SVGs anastomosed to small target vessels (<1.5 mm). We found significant differences in SVG patency and repeat-revascularization rates between groups T and L; however, no significant differences were found in the rates of mortality and bleeding complications requiring hospital admission.

One of the factors of SVG occlusion in the early postoperative period is endothelial injury of SVG. Endothelial injury activates the extrinsic coagulation cascade by tissue factor in the exposed subendothelium.[14] Furthermore, thrombosis at the site of the injured endothelium leads to a progressive increase in intimal fibrosis and hyperplasia and causes SVG occlusion.[15] Warfarin administration could suppress the over-activation of the extrinsic coagulation cascade and thrombosis. These are the reasons of our hypothesis that warfarin administration plus aspirin in the early postoperative period could improve the long-term patency of SVG.

Warfarin is a dose-dependent drug, and INR is a measurement of its efficacy. An INR value between 1.6 and 2.6 seems to prevent major ischemic or hemorrhagic events for those diagnosed with atrial fibrillation.[8] An INR value >1.6 is sufficient to evaluate the effect of warfarin, especially the prevention of SVG occlusion due to thrombus formation. There are some studies that report the advantages of warfarin administration for treating ischemic heart disease. Rothberg et al.[7] reported that the cardiovascular benefits of warfarin (INR >2.0) plus aspirin outweigh the bleeding risks, while Kato et al.[9] pointed out the importance of warfarin (INR >2.0) plus

aspirin after LAD reconstruction with endarterectomy using left ITA in preventing graft occlusion. In view of these findings, we performed administration of therapeutic-dose warfarin (INR >1.6) postoperatively.

The Post-CABG trial[6] found no significant differences in angiographic outcomes between the low-dose warfarin and placebo groups. In the study, the mean INR was 1.4 in the warfarin group and 1.05 in the placebo group. We speculated that INR <1.6 is not sufficient to evaluate the effect of warfarin, especially for preventing SVG occlusion. The authors of the Post-CABG stated "we cannot conclude that more aggressive anticoagulation would not be beneficial", which reflects our speculation.

Maintaining a patient's INR within the therapeutic range is a well-established predictor of adverse events such as major hemorrhage or thromboembolism.[16] The mean and standard deviation of INR in Group T and Group L were 2.1 ± 0.3 and 1.4 ± 1.2, respectively. TTR is a recommended quality measure for warfarin administration management in outpatients. There are several methodologies for calculating TTR. In this study, the INR data were calculated as described by Rosendaal et al.,[17] the findings of which have been adopted in many large clinical trials.[18] The number of patients in group L made up approximately half of the sample in our study (94 of 199 [47%]). Patients with INR >70% of TTR are considered to be in good control, while 60% or lower are considered to be at a loss of benefit from warfarin.[19,20]

Several recent randomized clinical trials and meta-analyses have suggested that dual anti-platelet therapy (DAPT) may be more effective in preventing SVG occlusion than aspirin alone. Due to the mechanism of action of P2Y12 inhibitors, combining clopidogrel with aspirin may efficiently prevent thrombus formation. Clopidogrel has also been reported to inhibit the process of intimal hyperplasia and smooth muscle hyperplasia in experiments on animal models of thrombus formation.[21,22] In view of these reasons, DAPT has been suggested to be more beneficial in preventing SVG occlusion compared to aspirin alone,[23,24] which is similar to our theory. In our study, 3 patients (2.9%) in group T and 5 patients (5.4%) in group L were administered DAPT in addition to warfarin. Because these numbers are small, no significant difference was found between the two groups (p = 0.684). Antiplatelet agents are dose-dependent drugs, and their blood levels can be affected by age, renal function, and other factors. Nevertheless, there is no measurement of the efficacy of DAPT, such as an INR value. We assume that this is the reason for the high incidence of major bleeding complications reported for DAPT.[25] In addition, there are no antagonists for antiplatelet agents. Although DAPT has been suggested to be beneficial in preventing SVG occlusion, we prefer warfarin to DAPT postoperatively because warfarin plus aspirin can be more safely administered than DAPT.

The target vessel diameter was the most relevant for SVG patency in this study. Desai et al.[26] reported that the distal run-off strongly correlated with the size of the distal target vessels, and small target vessel size adversely affected the graft patency. Similarly, Nakano et al. reported that recipient coronary artery diameter <1.5 mm was an independent predictor of graft failure,[27] which corresponds to the results of our study. Although the target vessel diameter is closely related to graft patency, there are certain circumstances in which anastomosis must be performed despite unfavorable target vessel diameters. **Figure 2** shows that therapeutic-dose warfarin (INR >1.6) plus aspirin tends to be more effective for improving SVG patency when it is anastomosed to a small target vessel. These results suggest that warfarin administration is strongly recommended, especially for SVGs anastomosed to a small target vessel.

Bleeding is the most important complication of warfarin administration. In a meta-analysis, after myocardial infarction or acute coronary syndrome,[7] the annualized risk for major bleeding in the warfarin (INR >2.0) plus aspirin group ranged from 0.6% to 18.0%. In this study, the annualized risk for bleeding resulting in admission was 1.2% in group T and 1.9% in group L, showing no significant difference between the two groups. Jun et al.[28] reported that the risk of bleeding was higher among patients with reduced kidney function during the first 30 days of treatment with warfarin. However, there was no significant difference in the incidence of bleeding complications among patients stratified according to their kidney function (p = 0.697) in this study. We experienced a case of gastrointestinal bleeding due to high INR during the onset of acute kidney insufficiency. We concluded that patients with acute kidney insufficiency should be carefully monitored for bleeding complications during treatment with warfarin and should not hesitate to stop warfarin administration.

A systematic review showed that it is controversial which proximal anastomosis devices improve SVG patency and the risk of SVG occlusion is lower in sequential grafts than individual grafts.[1,3,4] Although the condition was different for each anastomosis, there was

no significant difference in the influence of proximal anastomosis device and graft design between two groups.

SVG occlusion in the early to mid-term postoperative period is more commonly associated with a shift from thrombosis to atherosclerotic changes. Although many theories exist,[2,3,29] the precise cause of this shift remains unknown. Optical coherence tomography (OCT) is a useful imaging modality to determine the nature of angiographically ambiguous lesions. OCT can assess fibrous, fibroatheromatous, and residual thrombi in the SVG lumen,[30] which can be effectively managed by antithrombotic therapy such as warfarin. In clinical practice, we have encountered a patient whose coronary artery stenosis due to thrombosis was diagnosed using OCT. The patient was successfully administered antithrombotic drugs to avoid unnecessary PCI. It is suggested that a detailed analysis of SVG lesions with OCT in the mid-term postoperative period may provide new insights for improving SVG patency.

In this study, we demonstrated that strict administration of therapeutic-dose warfarin (INR >1.6) over a year improved the SVG patency and decreased the repeat-revascularization rates. Endothelial injury of SVG and activation of subsequent thrombosis occur in the first year after CABG,[2–4] for which reason, we have administered warfarin plus aspirin aggressively for 1 year. Further research is required to investigate the effectiveness of warfarin administration for a more extended period of over 1 year postoperatively.

There are several limitations to this study. The first and most important limitation is its retrospective and observational design. The second limitation is that all the data were collected at a single institution using a small sample, and the surgeries were performed by a single surgeon. There are several potential biases for patient conditions, because patients with a small number of distal anastomoses or younger patients are less likely to receive SVGs, and patients with reduced renal function could not undergo angiographic examination postoperatively. Furthermore, there may be discrepancies among individuals in terms of their responses to warfarin, because the absorption of warfarin is affected by diet and intestinal conditions. Lastly, although the hypothesis was based on the past reports, the pathological changes of SVG were not investigated in this study, and further research is required.

Conclusion

Therapeutic-dose warfarin at an INR >1.6 plus aspirin for the first year after CABG would be effective to improve the long-term patency of SVG and decrease the repeat-revascularization rate with no change in the rates of mortality and bleeding complications requiring hospital admission.

Disclosure Statement

The authors declare no conflicts of interest in association with the present study.

References

1) Head SJ, Milojevic M, Taggart DP, et al. Current practice of state-of-the-art surgical coronary revascularization. Circulation 2017; **136**: 1331–45.
2) Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation 1998; **97**: 916–31.
3) Maleki ND, Afshar AE, Parikh PB. Management of saphenous vein graft disease in patients with prior coronary artery bypass surgery. Curr Treat Options Cardiovasc Med 2019; **21**: 12.
4) Gaudino M, Antoniades C, Benedetto U, et al. Mechanisms, consequences, and prevention of coronary graft failure. Circulation 2017; **136**: 1749–64.
5) Kulik A, Ruel M, Jneid H, et al. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. Circulation 2015; **131**: 927–64.
6) Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997; **336**: 153–62.
7) Rothberg MB, Celestin C, Fiore LD, et al. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med 2005; **143**: 241–50.
8) Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk, The Medical Research Council's General Practice Research Framework. Lancet 1998; **351**: 233–41.
9) Kato Y, Shibata T, Takanashi S, et al. Results of long segmental reconstruction of left anterior descending artery using left internal thoracic artery. Ann Thorac Surg 2012; **93**: 1195–200.
10) Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovas Surg 2014; **148**: e1–132.

11) Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. Intern Med 2001; **40**: 1183–8.
12) Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996; **28**: 616–26.
13) Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013; **48**: 452–8.
14) Verrier ED, Boyle EM. Endothelial cell injury in cardiovascular surgery. Ann Thorac Surg 1996; **62**: 915–22.
15) Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation 1998; **97**: 916–31.
16) Ansell J, Hirsh J, Dalen J, et al. Managing oral anticoagulant therapy. Chest 2001; **119**: 22S–38S.
17) Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; **69**: 236–9.
18) White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 2007; **167**: 239–45.
19) Morgan CL, McEwan P, Tukiendorf A, et al. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. Thromb Res 2009; **124**: 37–41.
20) Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv 2018; **2**: 3257–91.
21) Herbert JM, Dol F, Bernat A, et al. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. Thromb Haemost 1998; **80**: 512–8.
22) Harker LA, Marzec UM, Kelly AB, et al. Clopidogrel inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. Circulation 1998; **98**: 2461–9.
23) Hesterberg K, Rawal A, Khan S, et al. A meta-analysis comparing aspirin alone versus dual antiplatelet therapy for the prevention of venous graft failure following coronary artery bypass surgery. Cardiovasc Revasc Med 2020; **21**: 792–6.
24) Alexander JH. Ticagrelor following coronary artery bypass grafting: for better vein graft patency or better patient outcomes? JAMA 2018; **319**: 1661–2.
25) Gupta S, Belley-Cote EP, Panchal P, et al. Antiplatelet therapy and coronary artery bypass grafting: a systematic review and network meta-analysis. Interact Cardiovasc Thorac Surg 2020; **31**: 354–63.
26) Desai ND, Naylor CD, Kiss A, et al. Impact of patient and target-vessel characteristics on arterial and venous bypass graft patency: insight from a randomized trial. Circulation 2007; **115**: 684–91.
27) Nakano J, Okabayashi H, Noma H, et al. Early angiographic evaluation after off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2013; **146**: 1119–25.
28) Jun M, James MT, Manns BJ, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ 2015; **350**: h246.
29) Shuhaiber JH, Evans AN, Massad MG, et al. Mechanisms and future directions for prevention of vein graft failure in coronary bypass surgery. Eur J Cardiothorac Surg 2002; **22**: 387–96.
30) Brown EN, Burris NS, Gu J, et al. Thinking inside the graft: applications of optical coherence tomography in coronary artery bypass grafting. J Biomed Opt 2007; **12**: 051704.