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The roles of CHA2DS2-VASc score and blood inflammatory parameters in predicting the patency of saphenous vein grafts in patients with coronary artery bypass graft surgery

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ABSTRACT

Objective: Coronary artery bypass graft (CABG) surgery is a common treatment method in which saphenous vein grafts (SVG) and arterial grafts are used together in severe coronary artery disease. The CHA2DS2-VASc score is used to predict thromboembolic events in non-valvular atrial fibrillation as well as to predict prognosis in cardiovascular events. In this study, we planned to research the relation between CHA2DS2-VASc score and postoperative SVG patency rates in patients undergoing CABG.

Materials and Methods: One hundred seventeen patients with angina after CABG surgery who underwent coronary angiography were analysed retrospectively. Stenosis of 50% or more in at least one saphenous vein graft was accepted as saphenous vein graft disease (SVGD). We compared these patients in two groups concerning the presence of 50% or more stenosis in the SVG. These two groups were; Group 1 (n = 66); with saphenous vein graft disease, Group 2 (n = 51) without saphenous vein graft disease, respectively.

Results: A total of 117 patients participating in the study. Sixty-six patients in group 1 had SVGD (Mean age: 68.13±8.22, 60.6% male). Fifty-one patients in group 2 did not have SVGD (Mean age: 66.92±9.44, 72.5% male). The mean CHA2DS2-VASc score was significantly higher in group 1 compared to group 2. [5 (2-7) vs. 2 (1-7), respectively, P<0,001]. As a result of multivariate analysis, CHA2DS2-VASc score (OR: 5.263, CI 95%: 2,176- 12,728, P<0.001) and SII (OR: 1.236, CI 95%: 1,120-2,955, P=0.007) were determined as independent predictors for predicting SVGD

Conclusion: In the light of the results we have found, the CHA2DS2-VASc score and SII, which are easy to calculate in daily practice, can help us in predicting SVGD.

Keywords: CHA2DS2-VASc score, saphenous vein graft patency, systemic inflammation index

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INTRODUCTION

Coronary artery bypass graft surgery (CABG) is still the most preferred treatment method in left main coronary artery and multi-vessel disease. Although saphenous vein grafts (SVG) are easy to surgically remove, long-term patency rates are low. While the stenosis rate in saphenous vein grafts is 15% in the first year after surgery, this rate reaches 50% in the 10th year (1). Many factors can cause saphenous vein graft disease (SVGD), classic risk factors such as smoking, hypertension, dyslipidaemia, or small native vessel diameter (<2 mm) for CABG (2). In this patient group, surgical intervention has high morbidity and mortality, so most centers prefer percutaneous coronary intervention (PCI). While the mortality rate in re-do bypass surgery is 6-10%, the risk of death is 3-5 times higher than the first bypass surgery (3). Complication rates during the reoperation of SVG are also high. The plaques in the saphenous vein grafts are more fragile and have a higher thrombus burden. A no-reflow phenomenon that develops during PCI due to widespread thrombotic burden in SVG lesions increases the risk of myocardial infarction. Therefore, it is important to develop diagnostic methods that can predict this situation

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The CHA2DS2-VASc score is a clinical risk classification scale developed to estimate thromboembolic incidents in patients with atrial fibrillation (4). It was found that the CHA2DS2–VASc score, which was originally derived to estimate the risk of stroke in atrial fibrillation, could estimate adverse clinical outcomes independently in patients with coronary artery disease (5). It has been shown in various studies that low-grade persistent inflammation take part in the pathogenesis of atherosclerosis. Inflammation indices such as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and systemic immune-inflammation index (SII) were found to indicate saphenous vein graft patency in various studies (6).

In this study, we aimed to investigate the effects of CHA2DS2–VASc score and inflammatory parameters on SVGD.

MATERIAL and METHODS

Study Population

This current retrospective study was planned by analyzing the files of 117 patients with CABG who underwent coronary angiography (CAG) procedure between July 2019 and May 2021. Patients with chest pain and the patients' ischemia detected in imaging methods or stress tests were consecutively taken to coronary angiography. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

Basic demographic data, coronary angiography report, and blood test results were obtained from patients' medical records Inflammation indexes, respectively; NLR, platelet to lymphocyte ration (PLR), LMR, systemic inflammation response index (SIRI) and SII were calculated from peripheral cell counts obtained from complete blood count. Patients with diseases that could affect the immune system cell numbers in peripheral blood were excluded from the study. Patients with active infectious disease, sepsis, chronic inflammatory disease, severe chronic renal disease (glomerular filtration rate < 30ml/min/1,73m2), metallic prosthetic valve, or with malignancy were excluded from the study. We calculated the CHA2DS2-VASc score for each patient. CHA2DS2-VASc score was calculated as: (7).

Age 65-75 years: 1 point
Hypertension: 1 point
DM: 1 point
Congestive heart failure or left ventricular ejection fraction < 40%: 1 point
Female sex: 1 point
Vascular disease (defined as prior myocardial infarction, carotid artery disease, peripheral artery disease including intermittent claudication, and previous surgical or percutaneous intervention for abdominal aorta or vessels of upper or lower extremities): 1 point
History of stroke or transient ischemic attack: 2 points
Age ⩾ 75 years: 2 points

A stenosis of 50% or more in at least one saphenous graft was regarded as significant in CAG. We analysed the patients in two groups according to the results of angiography. These two groups were; Group 1 (n = 66); with saphenous vein graft disease, Group 2 (n = 51) without saphenous vein graft disease, respectively.

Patients with previously on antihypertensive therapy or whose three different blood pressure measurements in a sitting position average above 140/90 mmHg were considered hypertensive. In our study, diabetic patients were identified as fasting blood glucose ⩾126 mg/dl or hemoglobinA1c level ⩾6.5%, or coincidental blood glucose levels ⩾200 mg/dl, previous use of oral antidiabetic drugs or insulin. Heart failure was accepted as 40% or less of the ejection fraction. Cranial magnetic resonance images and cranial tomography results of the patients were retrospectively analysed in terms of stroke and transient ischemic attack. In terms of peripheral arterial disease, patient records, previous peripheral angiographies, computed topographies, or magnetic resonance angiographies were examined. Stenosis of 50% or more in these vascular structures was considered significant.

Evaluation of the coronary angiography

Coronary angiography images of all patients made with the Judkins technique in standard projections were examined in our tertiary cardiovascular center. In the angiography procedure, we visualized each vessel in at least two different projections. In some patients who could not have selective saphenous vein graft imaging, aortography was performed to better evaluate the SVG. The patients' coronary angiograms were perused by at least two independent practised invasive cardiologists who were blinded to the patients' clinical data. In our study, as in previous studies, stenosis of 50% or more in at least one saphenous graft was defined as SVGD.

Obtaining laboratory parameters

Before coronary angiography, all blood samples of the patients were obtained after a 12-hour fasting period. Complete blood counts were performed with an automatic blood cell analyser. Biochemical and cholesterol values were measured with an automatic device via the standard laboratory techniques.

Statistical analysis

All patient's data were analyzed by using SPSS 22.0 statistical Package program for Windows (SPSS Inc, Chicago, IL) .We evaluated whether the data were normally distributed with the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean ± SD, or median (minimum-maximum) according to their distribution. Categorical variables of the groups were compared with Chi-square or Fisher's exact test. Categorical variables were given as percentages. Normally distributed continuous variables were compared with the Student's t-test, and nonparametric variables were compared with the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was performed for determining the cut-off value of the CHA2DS2-VASc score for predicting the patency rate of SVGD. To identify different predictors on SVG patency univariate and multivariate analyses were performed. A p-value less than 0.05 were considered statistically significant. Spearman correlation analysis was performed for the SII and CHA2DS2-VASc score variables, which were found to be statistically significant in the multivariate logistic regression analysis.

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RESULTS

All basic demographic and clinical characteristics of the patients included in our study were summarized in **Table 1**. A total of 117 patients participated in the study. Sixty-six patients in group 1 had SVGD (Mean age: 68.13±8.22, 60.6% male). Fifty-one patients in group 2 did not have SVGD (Mean age: 66.92±9.44, 72,5% male). The mean CHA2DS2-VASc score was significantly higher in group 1 compared to group 2. [5 (2-7) vs. 2 (1-7), respectively, P<0.001]. Acetylsalicylic acid, beta- blocker and Ca–channel blocker use rates were similar between two groups. Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use rates were higher in group 2 (P=0.005). There was no difference between the two groups in terms of other demographic and clinical parameters. Admission laboratory parameters of the patients were summarized in **Table 2**. Hemoglobin, platelet, creatinine, blood lipid parameters, white blood cell, neutrophil, monocyte, mean platelet volume, red cell distribution width and NLR values were similar between two groups. Lymphocyte counts were statistically significantly lower in group 1 (P<0.001). Platelet-to-lymphocyte ratio, SII, SIRI and LMR values were statistically significantly in group 1 (P<0.001, P<0.001, P=0.018 and P<0.001, respectively).

Logistic regression analysis was performed to evaluate the predictive value of certain parameters for predicting SVGD. In univariate analysis; CHA2DS2-VASc score (OR [odds ratio] 3.301, 95% CI [confidence interval]: 1.877-5.805, P<0.001), ACE-I/ARB use (OR: 0.845, 95% CI: 0.690-0.983, P=0.008), low lymphocyte count (OR: 0.672, 95% CI: 0.504-0.726, P<0.001), PLR (OR: 1.297, 95% CI: 1.096-1.442, P<0.001), SII (OR: 1.448, 95% CI: 1.127-1.902, P <0.001), SIRI (OR: 0.804, 95% CI: 0.578-0.916, P=0.021) and LMR (OR: 0.443, 95% CI: 0.274-0.685, P <0.001) values were found to be significantly correlated with the development of SVGD. As a result of multivariate analysis, CHA2DS2-VASc score (OR: 5.263, CI 95%: 2.176- 12.728, P<0.001) and SII (OR: 1.236, CI 95%: 1.120-2.955, P=0.007) were determined as independent predictors for predicting SVGD (**Table 3**).

In ROC curve analysis, we showed that at a cut-off value of ⩾3.5, the CHA2DS2-VASc score exhibited 60% sensitivity and 50% specificity for detecting SVGD.[area under ROC curve = 0.645 95% CI:0.531-0.759 , P =0.019] (Figure 1). In Spearman correlation analysis there was a mild positive correlation between SII and CHA2DS2-VASc score (r= 0.301, P=0.004).

Table 1: Baseline demographic and clinical characteristics of the groups

Variables	Group 1 (n=66)	Group 2 (n=51)	*P-value*
Age (years)	68.13±8.22	66.92±9.44	0.473ł
Male gender, n (%)	40 (60.6%)	37 (72.5%)	0.138*
Heart failure, n (%)	15 (22.7%)	5 (9.8%)	0.127*
COPD, n (%)	7 (10.6%)	9 (17.6%)	0.372*
Stroke, n (%)	2 (3%)	1 (1.9%)	0.844*
Hypertension, n (%)	62 (95.4%)	44 (86.2%)	0.328*
Diabetes mellitus, n (%)	36 (54.5%)	23 (45%)	0.254*
CHA_2DS_2-VASc score	5 (2-7)	2 (1-7)	<0.001γ
Acetylsalicylic acid use, n(%)	66 (100%)	51 (100%)	1.000
Beta blocker use, n (%)	55 (83.3%)	49 (96%)	0.141*
Ca–channel blocker use, n (%)	23 (34.8%)	20 (39.2%)	0.497*
ACE-I/ARB use, n (%)	44(66.6%)	47(92.1%)	0.005*

*Chi square test (percentage), ł Independent samples T-test (mean ± standard deviation), γ Mann-Whitney U test (median, minimum-maximum), COPD: Chronic obstructive pulmonary disease, OAD; Oral antidiabetic drugs, ACE-I; Angiotensin-converting enzyme inhibitor, ARB; Angiotensin receptor blocker.

Table 2: Laboratory parameters of the patients

Variables	Group 1 (n=66)	Group 2 (n=51)	*P-value*
Hemoglobin (g/dl)	12.4±2.1	13.3±1.9	0.154ł
Platelet count($\times10^3$/µL)	238.4±53.1	219.9±53.7	0.093ł
Creatinine (mg/dl)	0.92 (0.52-8.44)	0.98 (0.56-7.33)	0.696γ
Total cholesterol (mg/dl)	220.4±51.7	192.1±51.3	0.481ł
High density lipoprotein-cholesterol (mg/dl)	41.4±10.2	42.9±12.2	0.812ł
Low-density lipoprotein cholesterol (mg/dl)	105.9±53.7	106.7±45.9	0.693ł
Triglyceride(mg/dl)	143.5(44-487)	149.5 (40-490)	0.856γ
High sensitivity C-reactive protein (mg/dl)	6.5 (0.41-180)	5.1 (0.34-256)	0.292γ
White blood cell ($\times10^3$/µL)	8.3 (4.9-17.6)	7.8(5.1-18.9)	0.304γ
Neutrophil ($\times10^3$/µL)	4.9 (3.1-14.2)	5.1 (2.9-11.3)	0.544γ
Lymphocyte ($\times10^3$/µL))	1.3 (0.5-2.7)	1.9 (0.7-3.9)	<0.001γ
Monocyte ($\times10^3$/µL)	0.5 (0.3-1.5)	0.5 (0.4-1.2)	0.197γ
MPV. fl	10.4±1.6	9.1±0.96	0.392ł
RDW	13.9 (11.1-16.9)	14.2 (10.7-23.2)	0.554γ
NLR	2.91 (0.82-21)	3.44 (0.94-14.7)	0.159γ
SII	1124.6 (463.9- 6784.7)	653.8(392.6-3471.4)	<0.001γ
SIRI	2.9 (1.2- 25.6)	1.9 (0.79-11.4)	0.018γ
PLR	216.4 (81.2-494.7)	123.7 (56.5-380)	<0.001γ
LMR	1.8 (0.4-5.2)	2.7 (1.2-6.9)	<0.001γ

γ Mann-Whitney U test (median, minimum-maximum), ł Independent samples t-test (mean ± standard deviation), MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil- to- lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PLR: Platelet-to- lymphocyte ratio, LMR: Lymphocyte - to-monocyte ratio

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Table 3: Univariate and multivariate logistic regression analysis to identify independent predictors of saphenous vein graft disease

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	***P- value***	**OR (95% CI)**	***P- value***
CHA_2DS_2-VASc score	3.301(1.877-5.805)	<0.001	5.263 (2.176-12.728)	<0.001
ACE-I/ARB use	0.845 (0.690- 0.983)	0.008	1.236 (0.879- 2.190)	0.364
Platelet	1.762 (0.794- 2.165)	0.114	--	--
Lymphocyte	0.672 (0.504- 0.726)	<0.001	--	--
NLR	1.090 (0.894- 1.133)	0.178	--	--
PLR	1.297 (1.096- 1.442)	<0.001	--	--
SII	1.448(1.127-1.902)	<0.001	1.236 (1.120-2.955)	0.007
SIRI	0.804 (0.578- 0.916)	0.021	--	--
LMR	0.433(0.274-0.685)	<0.001	0.799 (0.436-1.467)	0.470

SII: Systemic immune inflammation index, LMR: Lymphocyte- to-monocyte ratio

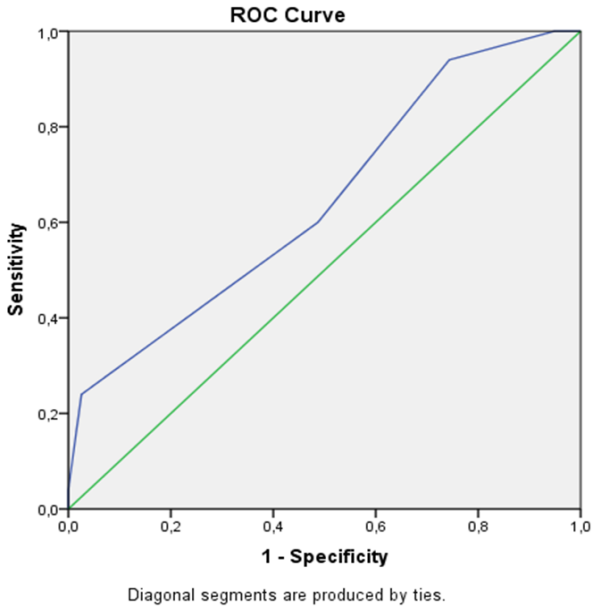

Figure 1: ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for CHA2DS2-VASc score for predicting saphenous vein graft disease. (Cut off: 3.5, AUC: 0.645, 95% CI:0.531- 0.759, P= 0.019, 60% sensitivity and 51.3% specificity)

DISCUSSION

CABG surgery has been the most effective treatment method used in the treatment of coronary artery disease for many years. CABG surgery has shortcomings such as SVGD, which may adversely affect the long-term outcomes. After CABG, long-term cardiovascular outcomes and recurrent symptoms depend on bypass graft patency and the rate of progression of disease in the native coronary arteries. SVG are the most commonly used grafts in CABG today. The rapid progression of the atherothrombotic process in saphenous vein grafts compared to arterial grafts affects patency rates in these grafts in the long term. Patency rates of the saphenous vein grafts at 1-, 5-, and 10-years are 93%, 74% and 41%, respectively. Occlusion rates in saphenous grafts were reported as 3.4% in the first 3 weeks and 12% in the first 6 months in some studies (**8, 9**). The causes of occlusion of saphenous vein grafts are thrombosis in the first 1-month acute stage, neointimal hyperplasia in the subacute stage (between 1 month and 12 months), and atherosclerosis in the late stage after 12 months, respectively. Saphenous graft revascularization rates after CABG vary between 8.6% and 10.4% annually. Despite developing stent technology and medical treatments, SVGD still remains a clinical problem that can't be completely prevented.

Patency rates of saphenous vein grafts are affected by the surgical technique used and the patient's clinical risk factors such as diabetes, hyperlipidemia, and smoking. Smoking increases calcification in saphenous vein grafts. It causes graft loss by increasing the synthesis of matrix metalloprotease 2 and 9 by smooth muscle cells. For example, the NO-touch technique used surgically minimizes vein damage and endothelial damage. Nitric oxide synthase activity of endothelial cells doesn't reduce in patients the No-Touch technique is used, in the endothelium also adhesion molecule synthesis and neutrophil adhesion to endothelium decrease.

Target natural coronary artery lesion size and condition, vascular diameter, and anastomosis all affect SVG patency rate. Arterialization occurs in saphenous grafts exposed to systemic pressure in the late period. In the first month after CABG, media layer thickening and neointimal hyperplasia occur in saphenous grafts. Neointimal hyperplasia doesn't cause significant stenosis but predisposes to atherosclerotic changes.

Artery wall is made up of thick elastic fibers and smooth muscle layer.

Arterial grafts such as; LIMA, radial artery graft, and right internal mammary artery (RIMA) are frequently used in CABG surgery. The use of left internal mammary artery (LIMA) in left anterior descending artery revascularization is the gold standard. Arterial grafts, especially LIMA resistant to atherosclerosis. These grafts are resistant to intimal hyperplasia and cellular migration because of the presence of internal elastic lamina on their walls and the absence of vasa-vasorum in the adventitia layers. In addition, the media layer is less prone to vasoconstriction due to the presence of fewer muscular cells and the thinness of this layer. Therefore, the LIMA graft has high disease-free survival rates and long-term patent rates (>90% in 10 years). The cause of late-stage failure in LIMA grafts is progressive atherosclerosis that develops in the native coronary artery distal to the anastomosis.

Many studies have shown that arterial graft selection improves long-term survival and reduces the frequency of percutaneous coronary intervention (**10, 11**). There is a complex low-grade ongoing inflammation in the pathogenesis of atherosclerosis. Many biomarkers of inflammation have been the focus of attention in predicting cardiovascular mortality (**4, 12**). Inflammatory markers such as C-reactive protein, fibrinogen, interleukin1, interleukin 6, lipoprotein (a) have also been found to be related with atherosclerosis in previous studies (**13, 14**).

Peripheral circulating leukocytes, monocytes, eosinophils and platelets play an important role in the initiation and maintenance of atherosclerosis (**15, 16**). Inflammation markers calculated from peripheral inflammation cells can help us in diagnosing SVGD. Stimulated White blood cells (WBCs) are both prone to adherence to the endothelial surface and, secreted hydrolytic enzymes, cytokines, and growth factors cause more vascular damage. WBCs contain five different types of immune cells. Leukocytes and neutrophils have important roles, especially in atherosclerosis. In the CAPRIE and SOLVD studies, high neutrophil levels and low lymphocyte ratios were related with increased poor cardiovascular outcomes (**17, 18**).

Several studies have found that high NLR and PLR, SII levels, as well as low LMR levels, may be beneficial to demonstrate the severity of coronary artery disease (**19**). In addition, NLR and PLR were found to be hemodynamically correlated in showing plaques with significant narrowing of the coronary artery (**20**). NLR has been associated in previous studies in predicting mortality after CABG and PCI and predicting in-stent restenosis (**21-23**).

Gurbuz et al. showed that preoperative NLR levels >4.32 increased cerebrovascular and cardiovascular adverse events in a retrospective study that included CABG patients (**24**). Likewise, high preoperative PLR levels were found to be significant in predicting complications after CABG. Gungor et al. found the ratio of postoperative AF to be high in the group with PLR level >119.3 after CABG (**25**). In our study, we also found significantly higher PLR levels in the group with SVGD.

It has been shown that SII predicts mortality in elderly patients with acute myocardial infarction undergoing PCI (**26**). Levels of SII >693.4X109 were associated with adverse cardiovascular outcomes after PCI (**27**). Agus et al. found that SII levels>2.314 to be related to high mortality in patients with infective endocarditis (**28**). SII was found to be better than LMR and PLR in predicting hemodynamically severe coronary artery disease (**29**).

In our study, we found SII, SIRI, PLR and LMR levels significantly higher in group 1 than group 2. Several studies have found that low LMR levels are related with poor endpoints in both critical limb ischemia and in-stent restenosis (**30, 31**).

The CHA2DS2-VASc score includes traditional risk factors such as hypertension, advanced age, and diabetes. These risk factors already contribute to thrombosis and atherosclerosis in coronary artery disease. Therefore, the CHA2DS2-VASc score can guide us in predicting saphenous vein graft disease. Also, it is widely used in daily clinical practice for stroke or systemic embolism risk stratification in nonvalvular atrial fibrillation, may provide useful information for risk assessment of patients with SVGD. Several studies have found the CHA2DS2-VASc score to be useful for risk stratification in patients without atrial fibrillation (**32, 33-35**).

In a study of 3184 patients with acute coronary syndrome (ACS), patients with a score $\geqslant$2 were related with a higher rate of MACE in the first year after discharge than those with a score <2 (36). In our study, we observed that CHA2DS2-VASc score $\geqslant$3.5 was highly significant in predicting SVGD. In another study, it was observed that patients hospitalized with the diagnosis of ACS had a higher rate of atherosclerotic burden in the coronary arteries and, the CHA2DS2-VASc score was higher in these patients (**37**). Ünal et al. found that a CHA2DS2-VASc score of 2 or higher increased the risk of stent thrombosis (**38**). The CHA2DS2-VASc score was related with no reflow and in-hospital death in patients undergoing PCI in another study (**39**).

Our study covered a small group of patients. Our study had a retrospective, single centre design. Instead of taking a complete blood count one time from patients and calculating indices from these measurements at admission, it would be more appropriate to take an average of more than one blood count. The effect of patients with atrial fibrillation on study outcomes was not examined in the study. Therefore, randomized controlled prospective, great sample size studies are needed.

CONCLUSION

CHA2DS2-VASc score and SII are two important markers for predicting SVGD disease. Patients with high SII and CHA2DS2-VASc score should be followed closely after CABG for graft failure, and arterial grafts may be preferred more in this patient group.

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