Cardiac Surgery

Global Risk Classification Predicts the Clinical Outcomes of Patients with Significant Left Main Coronary Artery Disease Undergoing Coronary Bypass Surgery

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Background: The use of combined SYNTAX score and EuroSCORE to predict two-year cardiac mortality in de-novo left main coronary artery (LMCA) disease patients undergoing percutaneous coronary intervention (PCI) has been discussed. Whether the combination of these two parameters could also predict the clinical outcomes in de-novo LMCA patients undergoing bypass surgery remains unknown.

Method: From April 2003 to June 2008, 86 patients with de-novo LMCA disease undergoing coronary artery bypass surgery (CABG) were studied. Patients were divided into three subgroups of global risk classification (GRC), low-risk group (n = 44), intermediate-risk group (n = 28), and high-risk group (n = 14) according to their SYNTAX score and EuroSCORE. The baseline characteristics were compared between different risk subgroups of GRC. The differences of clinical outcomes in terms of major cardiovascular and cerebrovascular events (MACCEs) between different risk subgroups of GRC were compared.

Results: Compared with the low-risk group, the high-risk group showed a significantly higher proportion of myocardial infarction (50.0% vs. 18.2%), congestive heart failure (21.4% vs. 2.3%), and cardiogenic shock (7.1% vs. 0.0%; $p = 0.02$), higher SYNTAX score (48.7 ± 5.6 vs. 27.5 ± 6.8; $p < 0.01$), higher EuroSCORE (7.7 ± 1.9 vs. 2.7 ± 1.5; $p < 0.01$), a higher proportion of diabetes mellitus (85.7% vs. 43.2%; $p = 0.02$), prior stroke (28.6% vs. 4.6%; $p = 0.03$), and peripheral arterial occlusive disease (28.6% vs. 2.3%; $p < 0.01$), and lower ejection fraction (50.8 ± 17.4 vs. 66.5 ± 14.1, $p < 0.01$). Using multivariable Cox-regression proportional regression with the forward conditional method, the global risk classification (GRC) predicted long-term cumulative MACCEs ($p < 0.01$, HR: 4.45, 95% CI: 2.48-7.99). The Kaplan-Meier Curve with log-rank test displayed significant differences of long-term MACCEs ($p < 0.01$; $\chi^2 = 39.08$) between different subgroups of GRC.

Conclusion: The new GRC system effectively predicts long-term MACCEs of de-novo LMCA disease patients undergoing CABG.

Key Words: Coronary artery bypass surgery • EuroSCORE • Global risk classification • Left main coronary artery disease • SYNTAX score

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INTRODUCTION

Significant left main coronary artery (LMCA) disease is present in 5%-7% of patients undergoing coronary angiography and has the worst prognosis of any form of coronary artery disease (CAD).[1] Currently, the standard of treatment for LMCA disease is coronary artery bypass graft surgery (CABG).[2] However, articles

discussing factors predicting long-term results of CABG for this specific subgroup patients are limited. Recently, the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score has been developed as a combination of several validated angiographic parameters including the number of lesions and their functional impact, complexity, and location.[3] The SYNTAX score has been suggested to be a useful parameter in predicting clinical outcomes of patients in this specific subgroup undergoing CABG.[4] The EuroSCORE is a well-validated system used for predicting peri-operative risk, 30-day and 1-year mortality in CABG patients. It is composed of several parameters including pre-operative condition, heart function and multiple underlying comorbidites. However, the complexity of coronary arteries is not considered in EuroSCORE. Both EuroSCORE and SYNTAX score had been suggested to be useful in predicting long-term outcomes of LMCA patients undergoing CABG. Whether the combination of SYNTAX score and EuroSCORE can enhance the predictability remains unknown. A newly developed global risk classification (GRC) merging both the SYNTAX score and the EuroSCORE has been proven successful in improving the prediction of long-term cardiac mortality in LMCA patients receiving percutaneous coronary intervention (PCI).[5] However, its clinical value in LMCA patients undergoing CABG remains unknown.[6] We tested whether the GRC could be useful in predicting long-term outcomes of LMCA disease patients receiving CABG.

METHOD

Study design

From April 2003 to June 2008, a total of 94 patients with de-novo significant LMCA disease underwent CABG. All patients received only CABG without concomitant valvular repair or replacement surgery. Seven patients who presented with cardiogenic shock underwent emergent CABG. Three of them were excluded because percutaneous balloon angioplasty before the index CABG procedure to improve the coronary blood flow of the infarct-related artery had been performed. One of the seven shock patients was excluded because the right coronary artery was not engaged successful, and calculation of SYNTAX score was not possible. Four patients were excluded because the diagnostic coronary angiograms were missing. Thus, 86 patients were included in this study. The end of the follow-up period was April, 2009.

SYNTAX score

As previously described by Sianos et al., each coronary artery lesion producing 50% or greater luminal obstruction in vessels 1.5 mm or greater in diameter was separately scored and added to provide the overall SYNTAX score.[7] The SYNTAX score integrates the number of the lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the Leaman and colleagues and the morphologic features of each lesion.[4] All diagnostic coronary angiograms were calculated by one investigator (C. C. Wang).

Global risk classification system

The additive EuroSCORE was calculated according to the original methodology.[8] The GRC is a combination of both EuroSCORE and SYNTAX score. The Euroscore was stratified into three groups to identify different risks (low-risk: 0-3; intermediate-risk: 4-5; high-risk: $\geqq$ 6). The SYNTAX score was stratified into three groups according to tertiles (lowest tertile: < 28, intermediate tertile: 28-38, highest tertile: > 38). The GRC system was classified into three risk groups. The low-risk group was composed of patients with both low/intermediate EuroSCORE and low/intermediate SYNTAX score. The intermediate-risk group was composed of patients with high EuroSCORE or high SYNTAX score. The high-risk group was composed of patients with both high EuroSCORE and high SYNTAX score. The definition of GRC is presented in Figure 1.[5]

Assessment of clinical outcomes

Clinical outcomes were determined by medical records and telephone contact. Clinical follow-up duration was calculated from the date of the index procedure to the-end-of follow-up date if the patient was free from significant cardiovascular events or mortality, otherwise the follow-up duration was calculated from the index procedure to the date of the incidence of any major adverse cardiovascular and cerebrovascular events

		SYNTAX score		
		< 28	28-38	> 38
EuroSCORE	0-3	L	L	I
	4-5	L	L	I
	≧ 6	I	I	H

Figure 1. *Global risk classification (GRC) are classified as follows: Patients classified as high-risk group are those who have both EuroSCORE ≧ 6 and SYNTAX score > 38; patients classified as low-risk group (L) are those who have none of EuroSCORE ≧ 6 or SYNTAX score > 38; otherwise, patients are classified as intermediate-risk group (I).*

(MACCEs). MACCEs included all-cause mortality, myocardial infarction (MI), coronary artery revascularization and new onset of cerebrovascular events. All-cause mortality included both cardiovascular deaths (CV deaths) and non-cardiovascular related deaths (non-CV deaths). The clinical outcomes were evaluated with several end points. The primary end point was defined as the incidence of any MACCEs. The secondary end point was defined as the incidence of the composite of cardiovascular deaths (CV deaths), MI, revascularization, and stroke. The cause of death was considered as cardiovascular in origin unless otherwise specified. The definition of cerebrovascular event is any acute event related to impairment of the cerebral circulation that lasts for more than 24 hours and results in irreversible brain damage or permanent functional disability. Myocardial infarction is defined as the detection of a rise of cardiac biomarker (troponin I) values with > 1 value above 99th percentile of the upper reference limit together with evidence of myocardial ischemia with ≥ 1 of the following: clinical symptoms of ischemia; electrocardiogram changes indicative of new ischemia (new ST-T wave changes or new left bundle branch block); development of pathological Q waves in the electrocardiogram.[9,10]

Statistical analyses

Categorical variables were presented as percentage, and continuous variables were presented as mean ± standard deviation (SD). Fisher's exact test was used to analyze potential differences in all categorical variables between patient subgroups. One-way ANOVA was used to evaluate potential differences in all continuous variables. Univariable Cox proportional hazards regression model was used to evaluate potential predictors for long-term MACCEs. All variables with a probability value ≦ 0.1 in the univariable Cox proportional hazards regression model were then entered into the multivariable Cox proportional hazards regression model to determine independently predictive factors for long-term MACCEs. Spearman rank correlation was used to investigate the correlation between GRC, SYNTAX score, and EuroSCORE. Survival curves were estimated by Kaplan-Meier method. Differences in survival were compared using the log-rank test. The comparisons of discriminatory ability between GRC, SYNTAX score, and EuroSCORE in terms of long-term MACCE and the composite of CV deaths, recurrent MI, revascularization, stroke were performed with receiver operator characteristics (ROC) curve analysis. A probability value < 0.05 was considered statistically significant. All statistical analysis were performed using SPSS 15 (SPSS Inc., Chicago, IL).

RESULTS

All patients were divided into three different risk groups according to their individual SYNTAX score and EuroSCORE as described above. Differences in clinical characteristics between subgroups stratified according to GRC are summarized in Table 1. Higher proportions of myocardial infarction, congestive heart failure, cardiogenic shock and more diseased vessels were present in the high-risk group than in low-risk group. Significantly higher incidences of diabtes mellitus (DM), prior stroke, peripheral arterial occlusive disease, and lower ejection fraction were present in the high-risk group than in the low-risk group. Differences in all surgical characteristics between the subgroups are summarized in Table 2. The high-risk group of GRC had significantly higher SYNTAX score and EuroSCORE than the low-risk group of GRC (48.7 ± 5.6 vs. 27.5 ± 6.8; $p < 0.01$, 7.7 ± 1.9 vs. 2.7 ± 1.5; $p < 0.01$). The low-risk group of GRC had significantly more arterial graft numbers than the high-risk group of GRC (1.2 ± 0.6 vs. 0.9 ± 0.4; $p = 0.04$).

Table 1. Baseline characteristics of the study population

	Global risk classfication			p value
	Low-risk group (n = 44)	Intermediate-risk group (n = 28)	High-risk group (n = 14)	
Age	64.5 ± 8.3	64.9 ± 9.8	70.9 ± 7.4	0.05[a]
Male gender	37/44 (84.1%)	20/28 (71.4%)	9/14 (64.3%)	0.22[b]
Symptom				< 0.01[b]
Angina	24/44 (54.6%)	11/28 (39.3%)	2/14 (14.3%)	
Unstable angina	11/44 (25.0%)	6/28 (21.4%)	1/14 (7.1%)	
AMI	8/44 (18.2%)	7/28 (25.0%)	7/14 (50.0%)	
CHF	1/44 (2.3%)	2/28 (7.1%)	3/14 (21.4%)	
Cardiogenic shock	0/44 (0.0%)	2/28 (7.1%)	1/14 (7.1%)	
Diseased vessels				< 0.01[b]
Isolated LM	2/44 (4.6%)	1/28 (3.6%)	0/14 (0%)	
LM + 1-v-d	8/44 (18.2%)	1/28 (3.6%)	0/14 (0%)	
LM + 2-v-d	18/44 (40.9%)	3/28 (10.7%)	1/14 (7.1%)	
LM + 3-v-d	16/44 (36.4%)	23/28 (82.1%)	13/14 (92.9%)	
DM	19/44 (43.2%)	17/28 (60.7%)	12/14 (85.7%)	0.02[b]
HTN	28/44 (63.6%)	21/28 (75.0%)	10/14 (71.4%)	0.64[b]
Smoking	24/44 (54.6%)	17/28 (60.7%)	4/14 (28.6%)	0.15[b]
Renal impairment	2/44 (4.6%)	2/28 (7.1%)	2/14 (14.3%)	0.37[b]
ESRD	2/44 (4.6%)	1/28 (3.6%)	1/14 (7.1%)	1.00[b]
COPD	8/44 (18.2%)	5/28 (17.9%)	4/14 (28.6%)	0.66[b]
Prior revascularization	6/44 (13.6%)	3/28 (10.7%)	1/14 (7.1%)	1.00[b]
Prior MI	8/44 (18.2%)	6/28 (21.4%)	3/14 (21.4%)	0.94[b]
Prior stroke	2/44 (4.6%)	6/28 (21.4%)	4/14 (28.6%)	0.02[b]
PAOD	1/44 (2.3%)	10/28 (35.7%)	4/14 (28.6%)	< 0.01[b]
T-Chol	169.7 ± 47.1	178.2 ± 31.5	180.3 ± 27.7	0.56[a]
LDL-C	103.9 ± 38.3	112.2 ± 30.3	108.2 ± 19.3	0.59[a]
HDL-C	39.1 ± 10.5	38.6 ± 10.1	36.5 ± 7.0	0.69[a]
T-Chol/HDL	4.49 ± 1.17	4.82 ± 1.11	5.03 ± 1.10	0.23[a]
EF	66.5 ± 14.1	57.9 ± 14.2	50.8 ± 17.4	< 0.01[a]

AMI, acute myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LM, left main disease; PAOD, peripheral arterial occlusive disease; T-Chol, total cholesterol. a: one-way ANOVA; b: Fischer's exact test.

Table 2. Surgical characteristics of the study population

	Global risk classification			p value
	Low-risk group (n = 44)	Intermediate-risk group (n = 28)	High-risk group (n = 14)	
SYNTAX score	27.5 ± 6.8	38.9 ± 11.4	48.7 ± 5.6	< 0.01[a]
EuroSCORE	2.7 ± 1.5	5.0 ± 2.8	7.7 ± 1.9	< 0.01[a]
Graft number	2.0 ± 1.5	2.1 ± 0.4	2.1 ± 0.5	0.49[c]
Arterial grafts	1.2 ± 0.6	0.9 ± 0.4	0.9 ± 0.4	0.04[c]
Total arterialization	9/44 (20.5%)	0/28 (0%)	0/14 (0%)	< 0.01[b]
Complete revascularization	41/44 (93.2%)	22/28 (78.6%)	13/14 (92.9%)	0.18[b]
On pump/Off pump	31/13	22/6	12/2	0.49[b]
Admission days	28.4 ± 16.1	29.4 ± 21.0	42.3 ± 25.9	0.08[a]

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as proportions. a: one-way ANOVA; b: Fischer's exact test; c: Kruskal-Wallis one-way ANOVA analysis.

Nine of the 86 patients (10.5%) received total arterializations; all of these cases were low-risk group patients. Seventy-six of the 86 patients (88.4%) received complete revascularization. There was a trend towards longer hospital stay in the high-risk group than in the intermediate- and low-risk groups (42.3 ± 25.9 vs. 29.4 ± 21.0 vs. 28.4 ± 16.1; p = 0.08). The differences in long-term outcomes between different subgroups are summarized in Table 3. Higher rates of long-term MACCEs (p = 0.01) and myocardial infarction (p < 0.01) were seen in the high-risk group than in the low-risk group. The MACCEs are summarized in Table 4. Fourteen of the 86 patients died during the follow-up period. Seven patients died during the index hospitalization. Six of them died of septic shock. One of them died of cardiovascular cause. Seven patients died during the

Table 3. Long-term outcomes of the LM patients receiving surgical treatment

	Global risk classification			p value
	Low (n = 44)	Intermediate (n = 28)	High (n = 14)	
MACCE	5 (11.4%)	9 (32.1%)	10 (71.4%)	0.01[a]
CV deaths	0 (0.0%)	3 (10.7%)	0 (0.0%)	0.17[a]
Non CV deaths	2 (4.6%)	4 (14.3%)	5 (35.7%)	0.83[a]
MI	1 (2.3%)	6 (21.4%)	3 (21.4%)	< 0.01[a]
Stroke	1 (2.3%)	2 (7.1%)	2 (14.3%)	0.49[a]
Revascularization	2 (4.6%)	3 (10.7%)	3 (21.4%)	0.11[a]

CV deaths, cardiovascular deaths; LM, left main coronary artery disease; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction. a: Fischer's exact test.

Table 4. Causes of death during the follow up period

GRC	Gender	Age	EF	MACCEs	Time from the index procedure
L	F	65	89%	PTCA for ostial LAD and D1	27 months
L	M	67	64%	Traumatic intracerebral hemorrhage, death	30 months
L	M	66	78%	Acute ischemic stroke with left vertebral artery stenosis	36 months
L	M	65	77%	Hickmann catheter infection, septic shock, death	44 months
L	M	61	42%	MI, Graft occlusion, PTCA + Stent for LM to LCX with DES	13 months
I	M	71	55%	Periprocedural MI, Perforated DU with peritonitis, septic shock	13 days
I	M	66	74%	Periprocedural MI, CV death	11 days
I	M	70	45%	Periprocedural MI, stroke, and ventilator associated pneumonia, death	3 months
I	M	59	34%	PCI for stenotic venous graft, acute stroke attack	24 months
I	F	69	59%	Stroke, STEMI, CV death	27 months
I	F	61	71%	PTCA + Stent for LCX	21 months
I	M	67	53%	Pneumonia, ARDS, death	13 months
I	F	52	48%	PCI for ostial RCA, MI, Pneumonia and septic shock, death	11 months
I	M	67	39%	Recurrent MI, CV death	2 months
H	F	75	69%	Pneumonia, septic shock, acute renal failure	3 months
H	M	68	29%	Mediastinitis, septic shock	1 month
H	M	80	57%	Ventilator associated pneumonia, septic shock	2 months
H	M	70	36%	Mediastinitis, septic shock	3 months
H	F	66	38%	MI, PTCA + Stent for LM to ostial LAD	10 months
H	M	61	58%	PTCA for RCA	24 months
H	M	74	75%	Acute ischemic stroke, died of colon cancer	10 months
H	F	62	48%	MI	9 months
H	M	60	63%	PTCA for LAD	14 months
H	F	70	66%	MI	16 months

ARDS, adult respiratory distress syndrome; CV death, cardiovascular death; D1, first diagonal branch; DES, drug-eluting stent; DU, duodenal ulcer; EF, ejection fraction; F, female; GRC, global risk classification; H, high-risk group; I, intermediate-risk group; L, low-risk group; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; M, male; MACCEs, major cardiovascular and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transcoronary angioplasty; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction.

long-term follow-up period. Five patients died of non-cardiovascular causes, three of them of sepsis, one of colon cancer, one of intracerebral hemorrhage, and two of myocardial infarction.

Factors predicting long-term MACCE identified using univariable Cox proportional hazards regression model are presented in Table 5. With a p value $\leqq$ 0.1 in univariable analysis, GRC, SYNTAX score, Euro-SCORE, symptom, diseased vessels, DM, renal impairment, prior stroke, peripheral arterial occlusive disease (PAOD), ejection fraction (EF) were then identified to fit the multivariable Cox proportional hazards regression model. Using the forward conditional method, only GRC (Intermediate vs. Low, HR: 4.09, p = 0.01; High vs.

Table 5. Cox-regression proportional hazard model to determine the predictors of cumulative MACCE events

Univariable analysis	p value	Hazard ratio	95% confidence interval
GRC			
Intermediate-risk vs. low-risk group	0.01	4.09	1.36-12.23
High-risk vs. low-risk group	< 0.01	19.50	6.07-62.65
SYNTAX score	< 0.01	1.06	1.02-1.10
Euroscore	< 0.01	1.34	1.16-1.55
Age	0.56	1.01	0.97-1.06
Male gender	0.12	0.51	0.22-1.20
Symptom	0.06	1.41	0.99-2.03
Diseased vessels	0.03	2.25	1.08-4.70
DM	0.04	2.69	1.07-6.80
HTN	0.52	0.76	0.32-1.77
Smoking	0.93	0.96	0.43-2.15
Renal impairment	0.08	2.63	0.89-7.77
ESRD	0.11	2.72	0.80-9.19
COPD	0.61	1.29	0.48-3.47
Prior revascularization	0.89	0.90	0.21-3.84
Prior MI	0.79	1.15	0.43-3.08
Prior stroke	0.01	3.22	1.32-7.85
PAOD	0.05	2.47	1.02-5.99
T-Chol	0.97	1.00	0.99-1.01
LDL-C	0.45	1.00	0.98-1.01
HDL-C	0.18	0.97	0.92-1.02
T-Chol/HDL-C	0.25	1.23	0.87-1.75
EF	0.02	0.97	0.94-0.99
Total graft number	0.86	1.10	0.41-2.92
Arterial graft number	0.47	0.74	0.33-1.68
Total arterialization	0.22	0.04	0.00-6.72
Complete revascularization	0.69	1.35	0.32-5.73
Multivariable analysis with forward conditional method			
GRC			
Intermediate- vs. Low-risk group	0.01	4.09	1.36-12.23
High- vs. Low-risk group	< 0.01	19.50	6.07-62.65
Multivariable analysis with forward conditional method if GRC removed from the model			
EuroSCORE	< 0.01	1.30	1.12-1.51
SYNTAX score	0.01	1.05	1.01-1.09

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; ESRD, end-stage renal disease; GRC, global risk classification; HDL-C, high density lipoprotein; HTN, hypertension; LDL-C, low density lipoprotein; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; PAOD, peripheral arterial occlusive disease; T-Chol, total cholesterol.

Low, HR: 19.50, p < 0.01) independently predicted long-term MACCEs. However, the GRC was found to be significantly moderately correlated with SYNTAX score [p < 0.01, Rs (γ) = 0.71], and EuroSCORE [p < 0.01, Rs (γ) = 0.67], we thus removed GRC from the model. In a further analysis, the SYNTAX score [p = 0.01, 95% confidence interval (CI) of hazard ratio (HR): 1.01-1.09] and EuroSCORE (p < 0.01, 95% CI of HR: 1.12-1.51) were identified to be independent predictors for long-term MACCEs with the forward conditional method. Further analysis to identify independent factors predicting the composite of CV deaths, recurrent MI, revascularization, stroke; and non-CV deaths was performed and is presented in supplemental Table 1. Using univariable Cox proportional hazards regression model, GRC (p < 0.01), SYNTAX score (p < 0.01), EuroSCORE (p < 0.01), gender (p = 0.05), symptom (p = 0.09), diseased vessels (p = 0.07), and DM (p = 0.06), prior stroke (p < 0.01), PAOD (p = 0.09), EF (p = 0.05) were identified to fit into multivariable Cox proportional hazards regression model with the forward conditional method. GRC (Intermediate vs. Low, HR: 6.01, p < 0.01; High vs. Low, HR: 19.24, p < 0.01) was found to be the single predictive factor for the composite of CV deaths, recurrent MI, revascularization and stroke. If we removed GRC from the model, then SYNTAX score (HR: 1.05, p = 0.03), and EuroSCORE (HR: 1.29, p < 0.01) were identified to be independent predictors for the composite of CV deaths, recurrent MI, revascularization and stroke.

Kaplan-Meier survival curves of long-term MACCEs (overall estimated mean survival: 43.8 ± 2.4 months, 95% CI: 39.1 to 48.6 months), the composite of CV deaths, recurrent MI, revascularization and stroke (overall estimated mean survival: 47.7 ± 2.2 months, 95% CI: 43.3 to 52.0 months) with respect to GRC are presented in Figure 2. Using the log-rank test, the significant differences in terms of long-term MACCEs (Chi-Square = 26.05; p < 0.01) and the composite of CV deaths, recurrent MI, revascularization and stroke (Chi-Square = 30.24; p < 0.01) between different risk groups of the GRC were evident.

Table 6 demonstrates the discriminatory ability of GRC, SYNTAX score and EuroSCORE in predicting the risk of long-term cumulative MACCEs and the composite of CV deaths, recurrent MI, revascularization and stroke. In predicting long-term cumulative MACCE, the area under receiver operating characteristics curve (AUC) was higher in GRC than in EuroSCORE and SYNYAX score (0.76 vs. 0.74 vs. 0.70, respectively). In predicting the composite of CV deaths, recurrent MI, revascularization and stroke, the AUC was also higher in GRC than in EuroSCORE and SYNTAX score (0.73 vs. 0.70 vs. 0.69, respectively). The high-risk group of GRC predicted MACCEs with sensitivity of 41.7% and specificity of 93.6%. Using EuroSCORE ≧ 6 as cut-off value,

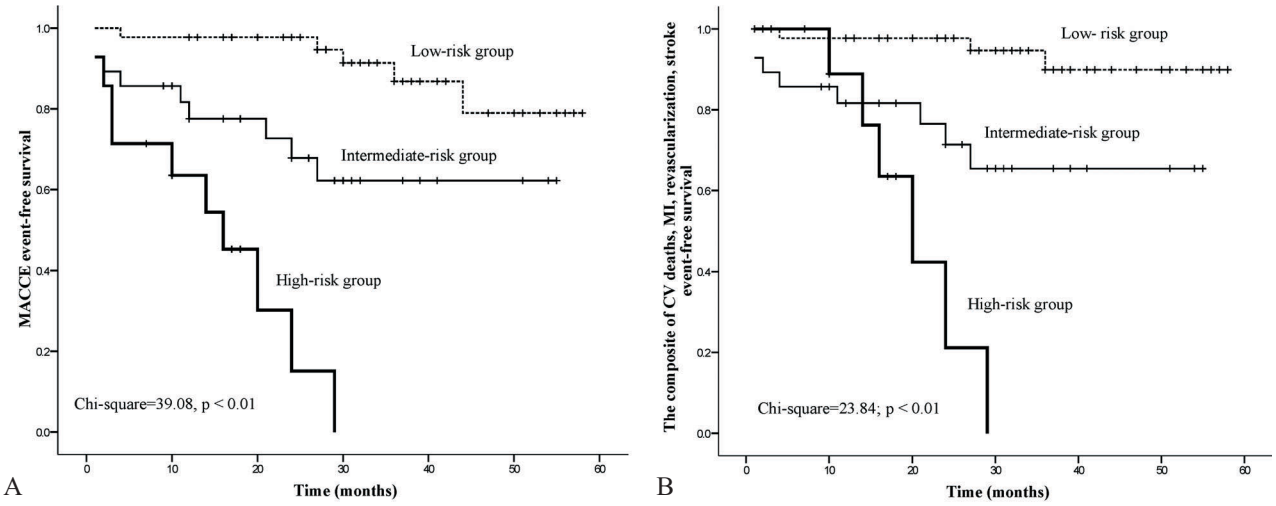

Figure 2. *Long-term cumulative incidence of MACCE (A) and the composite of CV deaths, MI, revascularization and stroke (B) with respect to different risk groups of GRC were estimated by Kaplan-Meier curves and compared with log-rank test. Significant differences in terms of the long-term MACCE-free survival (χ^2 = 39.08, p < 0.01) and the long-term outcome of the composite of CV deaths, MI, revascularization and stroke event-free survival (χ^2 = 23.84, p < 0.01) between different risk groups of GRC were found.*

Table 6. Discriminative ability of GRC, EuroSCORE, and SYNTAX score with respect to long-term MACCEs and the composite of CV deaths, MI, revascularization and stroke

Long-term MACCE	AUC	p value	95% confidence interval
GRC	0.76	< 0.01	0.64-0.88
EuroSCORE	0.74	< 0.01	0.63-0.85
SYNTAX score	0.70	< 0.01	0.58-0.83
The composite of CV deaths, MI, revascularization and stroke			
GRC	0.73	< 0.01	0.60-0.86
EuroSCORE	0.70	0.01	0.57-0.83
SYNTAX score	0.69	0.02	0.55-0.82

AUC, area under receiver operating characteristics curve; CV deaths, cardiovascular deaths; GRC, global risk classification; GRC, global risk classification system; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; ROC, receiver operating characteristics.

EuroSCORE predicted the MACCEs with sensitivity of 54.2% and specificity of 82.3%. Using SYNTAX score $\geqq$ 38.5 as cut-off value, SYNTAX score predicted the MACCEs with sensitivity of 66.7% and specificity of 74.2%. The high-risk group of GRC predicted the composite of CV deaths, recurrent MI, revascularization and stroke with sensitivity of 35.3% and specificity of 88.4%. Using EuroSCORE $\geqq$ 6 as cut-off value, EuroSCORE predicted the composite of CV deaths, recurrent MI, revascularization and stroke with sensitivity of 47.1% and specificity of 76.81%. The optimal cut-off value of SYNTAX score for predicting the composite of CV deaths, recurrent MI, revascularization and stroke was 38.5 (sensitivity = 70.6%, specificity = 71.0%).

DISCUSSION

The applicability of the SYNTAX score in predicting outcomes of CABG patients remains a matter of controversy. Generally, it is considered to be less valuable in predicting the clinical outcomes of CABG patients than in predicting long-term outcomes of PCI patients. That is justifiable because the SYNTAX score was initially developed to quantify the complexity of coronary artery disease, and it considered multiple variables which may adversely influence the clinical outcomes in patients undergoing PCI procedure.[11] Some variables such as bifurcation lesion, multiple tandem lesions, LM lesion, and chronic total occlusion, which may adversely affect the clinical outcomes of the PCI procedure, may be less significant for the surgical bypass procedure. However, there are also several factors, such as heavy calcification and diffuse lesion, which may influence the outcomes of the surgical bypass procedure. Current literature discussing the predictive value of the SYNTAX score to determine CABG patients' outcomes is diverse. One study found that higher SYNTAX score was significantly associated with poorer MACCE-free survival in patients with de-novo LMCA disease undergoing CABG.[4] Another study demonstrated that the SYNTAX score had poor prognostic value in predicting MACCEs in triple-vessel coronary artery disease patients undergoing CABG.[12] In our study, the SYNTAX score was an independent predictor of long-term MACCEs in LMCA disease patients receiving CABG, which is similar to previous reports. However, in our statistical result, the GRC, which includes both the clinical risk factors and the SYNTAX score, seemed to have better predictive value than the SYNTAX score alone in predicting long-term MACCEs in LMCA disease patients receiving CABG.

The EuroSCORE is a well-recognized and validated system for predicting clinical outcomes of CABG patients. Unlike the SYNTAX score, the additive EuroSCORE includes multiple clinical risk factors. Studies have indicated that the EuroSCORE system is a useful clinical tool in predicting immediate and long-term (up to 10 years) mortality in patients receiving coronary bypass surgery.[13,14] Another study also demonstrated that the EuroSCORE could be used to predict mid-term freedom from death and NYHA class III-VI in patients after combined valve and coronary bypass surgery (median

follow-up duration 23.7 months).[15] Recently, the EuroSCORE was shown to be useful in evaluating in-hospital mortality in coronary artery disease patients who underwent PCI.[16] In our study, using multivariable Cox proportional hazards regression model, we demonstrated that the EuroSCORE independently predicted long-term MACCEs in LMCA disease patients undergoing CABG. Therefore, there is rationale that the GRC, which combines the EuroSCORE and SYNTAX score, might be a better clinical risk-stratification tool than the SYNTAX score or the EuroSCORE alone in evaluating MACCEs. We proposed this idea because both SYNTAX score and EuroSCORE are complementary to each other. We believed both components have clinical value in predicting long-term outcomes of LMCA disease patients undergoing CABG.

The statistical analysis further confirmed our hypothesis. Using the Cox proportional hazards regression model with forward conditional method, GRC was shown to be the most powerful predictive factor in determining cumulative MACCEs. If GRC was removed as a covariate from this model, both additive EuroSCORE and SYNTAX score could be useful in predicting long-term MACCE in de-novo LMCA disease patients receiving CABG. One possible explanation that both the additive EuroSCORE and the SYNTAX score failed to be independent predictors when GRC was considered as a covariate is the significantly moderate correlation between the additive EuroSCORE, SYNTAX score and the GRC. In ROC analysis, the GRC had higher AUROC than those of EuroSCORE and SYNTAX score in predicting long-term MACCEs. All of these findings together indicate that the GRC seemed to be a stronger predictor than the SYNTAX score or the EuroSCORE alone in predicting long-term MACCEs and the composite of CV deaths, recurrent MI, revascularization and stroke. The result is reasonable because the combination of the SYNTAX score and the additive EuroSCORE (GRC) is composed of multiple angiographic and clinical variables that provides more information than just the SYNTAX score or the EuroSCORE alone. We believed the patients' long-term MACCEs are predicted better with a combination of multiple angiographic and clinical variables, rather than just the extent of coronary artery disease or only clinical comorbidities.

Limitations of the current GRC system

The EuroSCORE is a well-validated system, and a cut-off value of 6 is widely adopted to predict early post-operative deaths in patients after CABG. However, in the SYNTAX score system, an exact, simple, standard cut-off value to predict clinical outcomes is less well established. This reflects that the SYNTAX score is a newly developed scoring system, and its clinical application needs to be tested with more and larger clinical studies. Reviewing previous studies, Birim et al. found that SYNTAX score > 25 identified the highest MACCE incidence rates in LMCA patients undergoing CABG.[4] Capodanno et al. found a SYNTAX score > 34 identified LMCA patients who benefited the most from surgical revascularization treatment.[3] Van Gaal et al. demonstrated that a SYNTAX score > 17 predicted peri-procedural myocardial injury with sensitivity of 75% and specificity of 70% in patients undergoing PCI.[17] Capodanno et al. used GRC to predict cardiac mortality in LMCA patients undergoing PCI treatment. In that study, the SYNTAX score in the highest tertile > 27 and EuroSCORE > 6 identified the highest cardiac mortality rates.[5] Our study identified the highest SYNTAX score tertile as 38, which is higher than 27. In our study, the optimal cut-off value of SYNTAX score was 38.5 to predict the composite of CV deaths, MI, revascularization and stroke events. The average SYNTAX score in our study was higher than that in the study by Capodanno et al. (33.5 ± 11.6 vs. 24.8 ± 10.6, respectively). This reflects current real-world PCI practice, in which patients with de-novo LMCA disease and lower SYNTAX score are mostly treated with PCI, while those with higher SYNTAX score requiring technically more challenging strategies are usually referred for surgical treatment.

Study limitations

This was an observational study with small sample size. Further cohort study involving multi-center registry with larger sample size is mandatory before application of the GRC to clinical practice. However, the differences in long-term MACCEs between different risk groups of GRC were so obvious that it reached statistical significance even with small sample size. In addition, this study was designed to evaluate the clinical long-term outcomes after CABG in de-novo LMCA disease pa-

tients; thus, the clinical value of GRC in predicting outcomes in other specific CAD subgroups requires further confirmation. Because cases of missing coronary angiogram results were excluded, selection bias may have been introduced.

CONCLUSION

This study demonstrated that GRC is useful in predicting long-term MACCEs in LMCA disease patients undergoing CABG.

Supplement Table 1. Cox-regression proportional hazard model to determine the predictors of the composite of CV deaths, recurrent MI, revascularization, and stroke

Univariable analysis	p value	Hazard ratio	95% confidence interval
GRC			
Intermediate- vs. low-risk group	< 0.01	6.01	1.59-22.71
High- vs. low-risk group	< 0.01	19.24	4.49-82.50
SYNTAX score	< 0.01	1.06	1.02-1.10
EuroSCORE	< 0.01	1.34	1.13-1.60
Age	0.81	0.99	0.94-1.05
Male gender	0.05	0.38	0.14-1.00
Symptom	0.09	1.45	0.94-2.23
Diseased vessels	0.07	2.22	0.94-5.27
DM	0.06	2.90	0.95-8.92
HTN	0.21	0.54	0.21-1.42
Smoking	0.44	0.68	0.26-1.80
Renal impairment	0.40	1.89	0.43-8.27
ESRD	0.18	2.74	0.63-12.04
COPD	0.59	0.67	0.15-2.92
Prior revascularization	0.62	0.60	0.08-4.50
Prior MI	0.90	0.92	0.26-3.21
Prior stroke	< 0.01	4.08	1.50-11.06
PAOD	0.09	2.46	0.86-6.99
T-Chol	0.83	1.00	0.99-1.01
LDL-C	0.74	1.00	0.98-1.01
HDL-C	0.15	0.96	0.90-1.02
T-Chol/HDL-C	0.10	1.41	0.93-2.13
EF	0.05	0.97	0.94-1.00
Total graft number	0.69	1.26	0.40-3.98
Arterial graft number	0.56	0.75	0.28-1.99
Total arterialization	0.30	0.04	0.00-17.81
Complete revascularization	0.50	2.01	0.27-15.19
Multivariable analysis with forward conditional method			
GRC			
Intermediate- vs. low-risk group	< 0.01	6.01	1.59-22.71
High- vs. low-risk group	< 0.01	19.24	4.49-82.50
Multivariable analysis if GRC removed from the model			
EuroSCORE	< 0.01	1.29	1.08-1.55
SYNTAX score	0.03	1.05	1.00-1.09

GRC, global risk classification; DM, diabetes mellitus; HTN, hypertension; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; T-Chol, total cholesterol; LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; EF, ejection fraction.

REFERENCES

1. Seung KB, Park DW, Kim YH, et al. Stents versus coronary artery bypass grafting for left main coronary artery disease. *N Engl J Med* 2008;358:1781-92.
2. Kushner FG, Hand M, Smith SC, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). *Circulation* 2009;120:2290-1.
3. Capodanno D, Capranzano P, Elena M, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *J Am Coll Cardiol Interv* 2009;2:731-8.
4. Birim Ö, van Gameren M, Bogers AJ, et al. Complexity of coronary vasculature predicts outcomes of surgery for left main disease. *Ann Thorac Surg* 2009;87:1097-105.
5. Capoddano D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J* 2010; 159:103-9.
6. Wang CC, Chen WJ, Tsai FC, et al. In-hospital and long-term results of unprotected left main stenting versus coronary artery bypass grafting: a single center experience in Taiwan. *Acta Cardiol Sin* 2010;26:216-27.
7. Sianos G, Morel M-A, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *Eurointervention* 2005;1:219-27.
8. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999;15:816-22.
9. Lin YC, Hsu LA, Ko YS, et al. Impact of conventional cardiovascular risk factors on acute myocardial infarction in young adult Taiwanese. *Acta Cardiol Sin* 2010;26:228-34.
10. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation* 2007; 116:2634-53.
11. Lu TM, Jou YL, Chen YH, et al. The clinical significance of right coronary artery stenosis on the prognosis of patients with unprotected left main disease undergoing percutaneous coronary intervention. *Acta Cardiol Sin* 2011;27:14-20.
12. Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cadio Interv* 2009;73:612-7.
13. Biancari F, Kangasniemi K-P, Luukkonnen J, et al. EuroSCORE predicts immediate and late outcome after coronary artery bypass surgery. *Ann Thorac Surg* 2006;82:57-61.
14. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG. European system for cardiac operative risk evaluation predicts long-term survival in patients with coronary artery bypass grafting. *Eur J Cardiothrac Surg* 2004;25:51-8.
15. Kasimir MT, Bialy J, Moidl R, et al. EuroSCORE predicts midterm outcome after combined valve and coronary bypass surgery. *J Heart Valve Dis* 2004;13:439-43.
16. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart* 2009;95:43-8.
17. Van Gaal WJ, Ponnuthurai FA, Selvanayagam J, et al. The SYNTAX score predicts peri-procedural myocardial necrosis during percurtaneous coronary intervention. *Int J Cardiol* 2009;135: 60-5.