Impact of Hyperinsulinemia on Long-Term Clinical Outcomes of Percutaneous Coronary Intervention in Non-Diabetes Patients With Acute Myocardial Syndrome.

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Abstract

Background and Objectives: Hyperinsulinemia plays a key role in development of cardiovascular impairment in patients with Metabolic syndrome. The aim of this study was to evaluate the influence of hyperinsulinemia on long-term Clinical outcomes of percutaneous coronary intervention (PCI) in patients with acute myocardial syndrome.

Methods: Between March 2016 and January 2019, patients of ACS without diabetes mellitus and received primary PCI were enrolled. 368 patients were divided into low insulin group (n=157), medium insulin group (n=154) and high insulin group (n=157) according to tertiles of fasting insulin (FINS) level. The primary endpoint was major adverse cardiac events (MACE; all-cause death, non-fatal myocardial infarction, target vessel revascularization (TVR)) at 24 months. Second endpoint was angina-hospitalization.

Results: High insulin group had an unfavorable prognosis, with higher rate of MACE (34.39%) compared with low insulin group (22.29%) and medium insulin group (23.37%) at 24 months (P<0.05). This difference was mainly driven by the increase of TVR. High insulin group also had higher rate of angina-hospitalization than low insulin group. Multivariate logistic regression showed that high insulin level (OR2.636, 95%CI 1.378-5.023), small vessel lesion (OR2.636, 95%CI 1.378-5.023), bifurcation lesion (OR3.506, 95%CI 1.048-11.922) and Syntax score(OR1.116, 95%CI 1.054-1.182) were independent predictors of MACE in ACS patients after PCI

Conclusion: Hyperinsulinemia might be a valid predictor of clinical outcomes in ACS patients undergoing PCI.

Introduction

Metabolic syndrome (MetS) has a high prevalence around the world [1]. MetS is associated with the development of coronary atherosclerosis, plaque instability, and cardiovascular events in patients with or without type 2 diabetes [2–3]. The cores of metabolic syndrome are insulin resistance (IR) and hyperinsulinemia [4]. A new concept of selective insulin resistance indicates that tissues become resistant to insulin's effect on glucose transport but remain sensitive to its lipogenic effect [5]. IR may be compensatory in the body's response to prevent the metabolic syndrome. Hyperinsulinemia is more common than IR and may play a primary role in development of cardiovascular impairment in patients with MetS [6].

Our previous study demonstrated that hyperinsulinemia impaired functions of endothelial progenitor cells, which play a key role in maintaining endothelial function and vascular repairmen [7]. Other studies also indicated that hyperinsulinemia interfered with arteriolar vasodilation and NO bioavailability in obese, insulin resistant and healthy subjects [4, 8].

However, the impact of hyperinsulinemia on major clinical outcomes following percutaneous coronary intervention (PCI) is largely unknown. The aim of this study is to evaluate the impact of hyperinsulinemia on major clinical outcomes in patients with acute myocardial syndrome (ACS) undergoing PCI.

Methods

Study population

Between March 2016 and January 2019, patients with acute myocardial syndrome and received PCI were retrospectively enrolled. The including criteria is as following: 1. Patients of at least 18 years of age, who had ACS. ACS was defined as ST segment elevated myocardial infarction (STMEI), non-ST segment elevated myocardial infarction and unstable angina (UA) [9]. 2. Patients received primary PCI with drug-eluting stent (DES). The following conditions were excluded from the study: 1. Patients who were diagnosed with diabetes. Diabetes mellitus was defined according to the American Diabetes Association criteria [10]; 2. Patients without previously known diabetes but with glycated hemoglobin A1c(HbA1c) >6.5% on admission; 3. Angiography showed in-stent restenosis; 4.insulin or insulin sensitizer users. This study was approved by the ethics committee of Qinhuangdao First Hospital and all patients provided written informed consent.

Interventional procedure

Patients were administered 300 mg of aspirin and a loading dose of 300 mg Clopidogrel or 180mg Ticagrelor. Coronary angiograpy and percutaneous coronary intervention were performed in all patients by transradial or transfemoral approach. The angiographic findings were analysized by quantitative coronary angiography (QCA) system (GE QCA, Centricity AI 1000 – GE Mnet Version 4.1.15.07). With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter (MLD), lesion length were measured in diastolic frames.The Syntax score of each patient was calculated according to the results of coronary angiography.

Follow-up and study endpoints

All patients received aspirin (100 mg QD) and Clopidogrel (75 mg QD) or Ticagrelor (90mg BID). Patients underwent clinical observation for at least 36 months. Clinical follow up was performed at one month, six months, 12 months, 24 months.

The primary endpoint was major adverse cardiac events (MACE), including overall death, non-fatal myocardial infarction（MI）, target vessel revascularization (TVR) . MI was diagnosed by an elevation of serum creatine kinase or troponin three times the upper limit of normal, together with chest pain lasting more than 30 minutes [11]. TVR was defined as any repeat revascularisation of the stent treated vessel [11].

The second endpoint was angina pectoris requiring hospitalization.

Statistics analysis

All statistics analyses were performed by SPSS 17 (SPSS, Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation of the mean, and were compared by use of the one-way Anova test; The data of non normal distribution are transformed by logarithm. Categorical variables were compared with the χ^2 statistics or Fisher exact test. Multivariate logistic regression was used to estimate the predictors of MACE.MACE incidence rates of two year adverse cardiac events were estimated by the Kaplan-Meier method. A probability value < 0.05 was considered statistically significant. A probability value <0.05 was considered statistically significant.

Results

The enrolled patients were divided into three groups according to tertile of fasting insulin (FINS) level (low insulin group, FINS < 7.89μIU/mL; medium insulin group, 7.89μIU/mL ≤ FINS < 14.33μIU/mL; high insulin group, FINS ≥ 14.33μIU/mL). Baseline clinical characteristics were shown in Table 1. The three groups were balanced in age, gender, family history, hypertension, smoking, prior myocardial infarction and clinical presentation. There were no significant differences in laboratory characteristics such as left ventricular ejection fraction (LVEF), cholesterol, triglyceride, low density lipoprotein-cholesterol .Low insulin group had higher high density lipoprotein than high insulin group (P< 0.05). BMI, waistline, HOMA-IR and serum Urine in high insulin group were higher than that in low insulin group and medium insulin group. The angiographic and procedural characteristics were shown in Table 2. The target vessel had no significant difference among the three groups. QCA analysis revealed that high insulin group had longer lesion length and longer stents than low insulin group. Syntax scores were higher in high insulin group than that in low insulin group. High insulin group also had more target vessel stenosis and bifurcation lesions than low insulin group.

Table 1
Comparison of clinical characteristics according to FINS status

	Low insulin (n = 157)	Middle insulin (n = 154)	High insulin (n = 157)	F or χ^2	P value
age	62.59 ± 8.83	62.01 ± 9.15	59.21 ± 10.51	0.255	0.775
gender (M/F)	104/53	104/50	118/39	3.444	0.179
current smoker	77(49.04%)	77(50%)	76(48.41%)	0.080	0.961
family history	58(36.94%)	54(35.06%)	54(34.39%)	0.239	0.887
hypertension	102(64.86%)	95(61.68%)	101(64.33%)	0.406	0.816
prior MI	18(11.46%)	11(7.14%)	14(8.91%)	1.761	0.415
clinical presentation	17	14	24	4.337	0.362
STEMI	25	30	31	0.047	0.954
Non-STEMI	115	110	102	0.785	0.457
Unstable angina	74.44 ± 21.36	75.05 ± 19.23	75.21 ± 19.01	2.848	0.059
Grace score	4.45 ± 1.03	4.46 ± 2.22	4.26 ± 1.05	1.161	0.314
TC (mmol/L) TG (mmol/L)	1.72 ± 1.20	1.89 ± 1.98	2.16 ± 1.22*	4.514	0.012
LDL-C (mmol/L)	2.48 ± 0.81	2.46 ± 0.91	2.34 ± 0.81	0.405	0.667
HDL-C (mmol/L)	1.12 ± 0.24	1.06 ± 0.23	1.04 ± 0.22*	0.096	0.909
Glucose (mmol/L)	5.46 ± 0.78	5.42 ± 0.76	5.51 ± 0.90	835.16	0.000
HbA1c(%)	5.82 ± 0.75	5.86 ± 0.48	5.87 ± 0.41	121.732	0.000
Insulin(uIU/mL)	6.14 ± 1.41	10.68 ± 1.71**	17.69 ± 3.77**##	1.471	0.231
HOMA-IR	1.31 ± 0.60	2.14 ± 1.06**	3.62 ± 1.93**##	1.652	0.194
creatinine(μmol/L)	67.89 ± 14.59	67.24 ± 15.55	75.13 ± 68.69	0.879	0.416
Lg Troponin I	1.34 ± 0.31	1.27 ± 0.39	1.36 ± 0.32	1.188	0.306
Lg BNP	1.15 ± 0.79	1.88 ± 1.39	1.54 ± 1.03	6.511	0.002
HCY(mmol/L)	15.84 ± 8.93	17.64 ± 9.27	16.14 ± 8.82	53.53	0.000
Urine(mmol/L)	332.04 ± 84.97	336.78 ± 94.19	370.56 ± 101.70*#	5.811	0.003
BMI	24.31 ± 2.82		27.84 ± 3.41**##	0.971	0.380
Waistline(cm)	88.61 ± 11.33		94.93 ± 8.52**##		
LVD(mm)	48.98 ± 4.62		49.72 ± 4.76*		

FINS, fasting insulin; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial diameter; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; TC, cholesterol, ; TG, Triglyceride ; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide.

LAD(mm)	37.77 ± 5.49		39.21 ± 7.38		
LVEF(%)	65.53 ± 7.32		64.19 ± 8.88		
	Low insulin (n = 157)	**Middle insulin (n = 154)**	**High insulin (n = 157)**	**F or χ^2**	**P value**
		26.25 ± 2.72**		1.898	0.151
		92.66 ± 8.12*		0.979	0.388
		49.15 ± 4.36			
		38.25 ± 4.51			
		65.11 ± 7.13			

FINS, fasting insulin; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial diameter; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; TC, cholesterol, ; TG, Triglyceride ; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide.

Table 2
Comparison of angiographic and procedural characteristics according to FINS status

	Low insulin n = 157	Middle insulin n = 154	High insulin n = 157	F or χ^2	*P*
Target artery	8(5.09%)	6(3.89%)	7(4.45%)	0.261	0.877
Left main artery	95(60.51%)	84(54.54%)	90(57.32%)	1.134	0.567
Left anterior descending	22(14.01%)	25(16.23%)	23(14.64%)	0.319	0.853
Left circumflex artery	31(19.76%)	31(20.12%)	37(23.56%)	2.626	0.269
Right coronary artery	29 (18.47%)	33(21.42%)	45(28.66%)*	4.891	0.087
Bifurcation	117(74.52%)	119(77.27%)	124(78.98%)	0.895	0.639
Multivessel disease	2.91 ± 0.43	2.93 ± 0.49	3.01 ± 0.58	2.550	0.079
Target lesion	19.60 ± 8.54	20.36 ± 8.28	22.52 ± 9.39*	4.690	0.010
Reference diameter (mm)	89.19 ± 10.76	90.70 ± 7.72	91.75 ± 0.63*	3.240	0.040
Lesion length (mm)	10.81 ± 4.21	10.73 ± 3.97	12.79 ± 5.03*#	10.727	0.000
Diameter stenosis (%)	2.91 ± 0.41	2.98 ± 0.42	3.01 ± 0.41	2.121	0.146
Syntax Score	24.26 ± 14.71	25.71 ± 13.09	28.87 ± 12.24*	4.561	0.011
The characteristics of DES					
Diameter(mm)					
Length(mm)					

FINS, fasting insulin; DES: drug-eluting stent.

The baseline clinical characteristics of the patients stratified by the primary endpoint are summarized in Table 3. Compared with event-free group, patients with MACE had higher levels of FINS. Patients with MACE also showed higher rates of prior myocardial infartction, higher level of HOMA-IR, BMI, creatinine and waistline. As shown in Table 4, patients with MACE had smaller vessel diameter. At the mean while, patients with MACE showed higher Syntax scores and longer lesion length.

Table 3
Clinical characteristics of MACE and non-MACE group

	MACE group (n = 86)	Non-MACE (n = 382)	F or χ^2	P value
age	62.04 ± 9.44	61.14 ± 9.64	0.733	0.464
gender (M/F)	24/62	62/320	0.017	0.896
current smoker	46(53.48%)	184(48.16%)	2.830	0.093
family history	25(29.06%)	141(36.91%)	0.239	0.887
hypertension	54(62.79%)	250(65.44%)	0.278	0.598
prior MI	19(22.09)	24(6.28%)	21.03	0.000
clinical presentation	11	44	0.780	0.677
STEMI	13	73	0.047	0.954
Non-STEMI	62	265	1.230	0.219
Unstable angina	74.11 ± 14.78	76.84 ± 14.24	0.139	0.890
Grace score	4.18 ± 0.95	4.43 ± 1.61	0.616	0.539
TC (mmol/L) TG (mmol/L)	1.90 ± 1.02	1.93 ± 1.59	1.146	0.253
LDL-C (mmol/L)	2.37 ± 0.73	2.43 ± 0.86	0.635	0.526
HDL-C (mmol/L)	1.05 ± 0.18	1.08 ± 0.24	0.096	0.909
Glucose (mmol/L)	5.52 ± 0.66	5.45 ± 0.84	3.305	0.001
HbA1c(%)	5.77 ± 0.52	5.86 ± 0.58	2.458	0.014
Insulin(uIU/mL)	13.21 ± 4.15	11.09 ± 5.10	2.607	0.009
HOMA-IR	2.61 ± 0.95	2.30 ± 1.05	1.652	0.194
creatinine(μmol/L)	81.59 ± 11.59	67.57 ± 15.24	0.879	0.416
Lg Troponin I	1.31 ± 0.36	1.32 ± 0.34	1.476	0.141
Lg BNP	1.12 ± 0.63	1.22 ± 0.67	0.129	0.898
HCY(mmol/L)	18.11 ± 11.33	16.15 ± 8.41	2.520	0.012
Urine(mmol/L)	344.81 ± 106.27	346.43 ± 92.47	5.811	0.003
BMI	26.42 ± 4.15	25.98 ± 3.25	0.932	0.352

MACE: major adverse cardiac events; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial diameter; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; TC, cholesterol, ; TG, Triglyceride ; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide.

	MACE group (n = 86)	Non-MACE (n = 382)	F or χ^2	P value
Waistline(cm)	85.10 ± 10.69	79.01 ± 13.36	1.438	0.151
LVD(mm)	49.74 ± 4.91	49.16 ± 4.51	0.979	0.388
LAD(mm)	37.41 ± 3.84	38.58 ± 6.20		
LVEF(%)	63.59 ± 9.28	65.25 ± 7.43		

MACE: major adverse cardiac events; LVEF, left ventricular ejection fraction; LVD, left ventricular diameter; LA, left arterial diameter; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; TC, cholesterol, ; TG, Triglyceride ; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide.

Table 4
Angiographic and procedural characteristics of MACE and non-MACE group

	MACE group n = 86	Non-MACE group n = 382	F or χ^2	*P*
Target artery	7(8.13%)	14(3.66%)	3.279	0.070
Left main artery	54(62.79%)	215(56.28%)	1.216	0.270
Left anterior descending	11(11.62%)	59(15.44%)	0.389	0.533
Left circumflex artery	14(16.27%)	93(24.34%)	2.590	0.108
Right coronary artery	35 (40.69%)	72(18.84%)	19.002	0.000
Bifurcation	68(79.06%)	294(76.96%)	0.178	0.673
Multivessel disease	2.82 ± 0.41	2.94 ± 0.45	2.608	0.009
Target lesion	24.31 ± 9.06	20.06 ± 8.60	4.070	0.000
Reference diameter (mm)	92.68 ± 6.07	90.07 ± 9.43	2.457	0.014
Lesion length (mm)	47(54.65%)	59(15.44%)	56.591	0.000
Diameter stenosis (%)	14.11 ± 4.78	10.84 ± 4.24	6.292	0.000
Small vessel (diameter < 2.75mm)	2.93 ± 0.39	2.97 ± 0.42	2.455	0.015
Syntax Score	31.15 ± 12.33	25.24 ± 13.46	3.666	0.000
The characteristics of DES				
Diameter(mm)				
Length(mm)				

MACE: major adverse cardiac events; DES: drug-eluting stent.

Clinical follow-up was completed in all survival patients. Kaplan-meier survival analyses showed that the high insulin group had an unfavorable prognosis, with higher rates of MACE and angina hospitalization compared with the other two groups at 24 months (Fig. 1 and Fig. 2). As shown in Table 5, the incidence of the primary endpoint in high insulin group was significantly higher than that in low insulin group ($P < 0.05$). This difference was mainly driven by the increase in target vessel revascularization. However, the incidence of overall death, non-fatal MI during follow-up were similar among the FINS tertiles.

Table 5
Comparison of clinical outcomes after primary PCI during 24 months' follow-up according to FINS status.

	Low insulin n = 157	**Middle insulin n = 154**	**High insulin n = 157**	χ^2	*P*
Primary endpoint	23(22.29%)	24(23.37%)	39(34.39%)*#	6.935	0.031
All-cause MACE	8(5.09%)	7(4.54%)	7(4.45%)	1.134	0.567
death	7(4.45%)	9(5.84%)	10(6.36%)	0.319	0.853
non-fatal MI	8(5.09%)	8(5.19%)	22(14.01%)*#	10.999	0.004
TVR	13(8.28%)	12(7.79%)	25(15.92%)*#	6.177	0.046
Second endpoint					
Angina-hospitalization					

FINS, fasting insulin; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization; * compared with low insulin group, $P < 0.05$; # compared with middle insulin group, $P < 0.05$.

Multivariate analyses and predictors for MACE within 24 months after PCI are presented in table 6. After adjusting for confounding factors, multivariate logistic regression showed that the high insulin level, bifurcation lesion, small vessel lesion and Syntax score, were independent predictors of MACE in ACS patients after PCI (all $P < 0.05$).

Table 6 Predictors of major adverse events in patients undergoing PCI with ACS.

variables	Co-efficient	Odds ratio(95%CI)	*P* value
Hyperinsulinemia	2.636	1.378-5.023	0.003
Syntax score	1.116	1.054-1.182	0.000
Small vessel (<2.75mm)	2.536	1.048-6.135	0.039
bifurcation	5.506	2.543-11.922	0.000

Discussion

The main finding of this study is that high insulin level is associated with increased risk of MACE in ACS patients without diabetes mellitus. Hyperinsulinemia might be a valid predictor of clinical outcomes in ACS patients undergoing PCI.

Weakened insulin signalling or insulin resistance, together with the associated diminution in glucose transport, promotes compensatory increase of insulin that results in hyperinsulinemia [12]. As we know, insulin has double-phase effect on atherogenesis. Under physiological conditions, insulin stimulates the uptake of glucose and maintains glucose homeostasis [13]. But at hyper-physiological concentration, insulin stimulates proliferation of vascular smooth muscle cells and triggers inflammation [14]. Clinical and experimental evidence suggests that hyperinsulinemia can promote obesity and endothelial dysfunction [15-16].

Some previous studies explored the impact of insulin resistance on clinical outcomes of PCI, but the results were controversial. Yun et al analyzed 98 consecutive non-diabetic patients who underwent elective coronary angioplasty, and revealed that IR (HOMA index ≥2.6) was an independent predictor of in-hospital and 30 day MACE rates [17]. Hwang et al evaluated one year outcomes of 229 consecutive non-diabetic CAD patients treated with DES. The results found that despite worse trend in angiographic outcomes in the IR group (HOMA index ≥2.5), it was not translated into worse 1-year major clinical outcomes following PCI with DES as compared to the non-IR group [18].

The current study found that non-diabetic patients with hyperinsulinemia had increased MACE rate after undergoing PCI. As far as we know, this is the first study to discuss the direct impact of hyperinsulinemia on clinical outcomes of PCI. Actually, the incidence of MACE was mainly driven by the increase of target vessel revascularization.

In this study, we also found that patients with hyperinsulinemia had more angina-hospitalization than patients with low and middle insulin level. The mechanism of angina may be impaired microcirculation. Impaired coronary microcirculation is frequently observed in patients with insulin resistance and T2DM. This impairment is driven by reduced levels of bioavailable nitric oxide. Our previous study demonstrated that hyperinsulinemia impaired endothelial progenitor cell's function by down regulation of PI-3K/Akt/eNOS pathway [7]. NO is a key regulator in modulating endothelial function. Impaired NO reproduction may explain the results of the current study.

Limitations

This study has several limitations. First, it was a single center study, the sample size was relative small. Second, it is a retrospective but not a randomized controlled study, it may have selection bias. The third limitation was the relative short duration of 24 months of follow-up. It may be a limiting factor to evaluate important clinical effects of hyperinsulinemia. We still need more investigation and more time to testify the impact of insulin in patients undergoing PCI.

Conclusions

This study indicated an association between higher insulin levels and increased risk of MACEs in non-diabetes patients with ACS. Hyperinsulinemia might be a valid predictor of clinical outcomes in non-diabetes patients with ACS undergoing PCI.

Abbreviations

ACS: Acute coronary syndrome; BMI: Body mass index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHF: Congestive heart failure; CI: Confidence interval; CVD: Cardiovascular disease; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; HR: Hazard ratio; IR: Insulin resistance; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG:Triglyceride glucose.

Declarations

Acknowledgements

Authors' contributions

All authors were involved in the conception and design of the study and in the collection, analysis, and interpretation of the data. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by ethics commetee of Qinhuangdao first Hospital, Hebei Medical University. Given the retrospective nature of this study, the requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

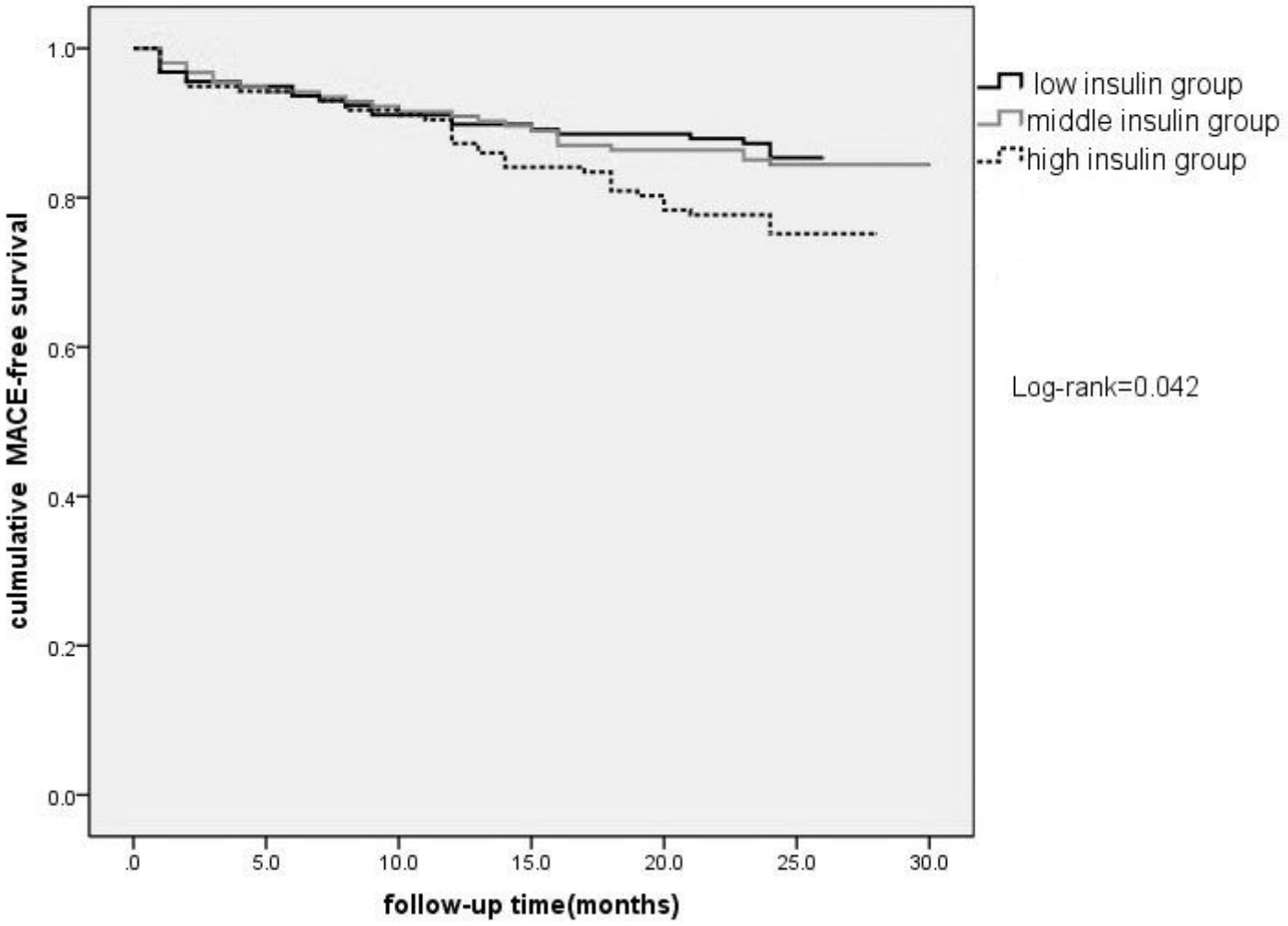

Figure 1

Clinical follow-up was completed in all survival patients. Kaplan-meier survival analyses showed that the high insulin group had an unfavorable prognosis, with higher rates of MACE and angina hospitalization compared with the other two groups at 24 months (Fig1).

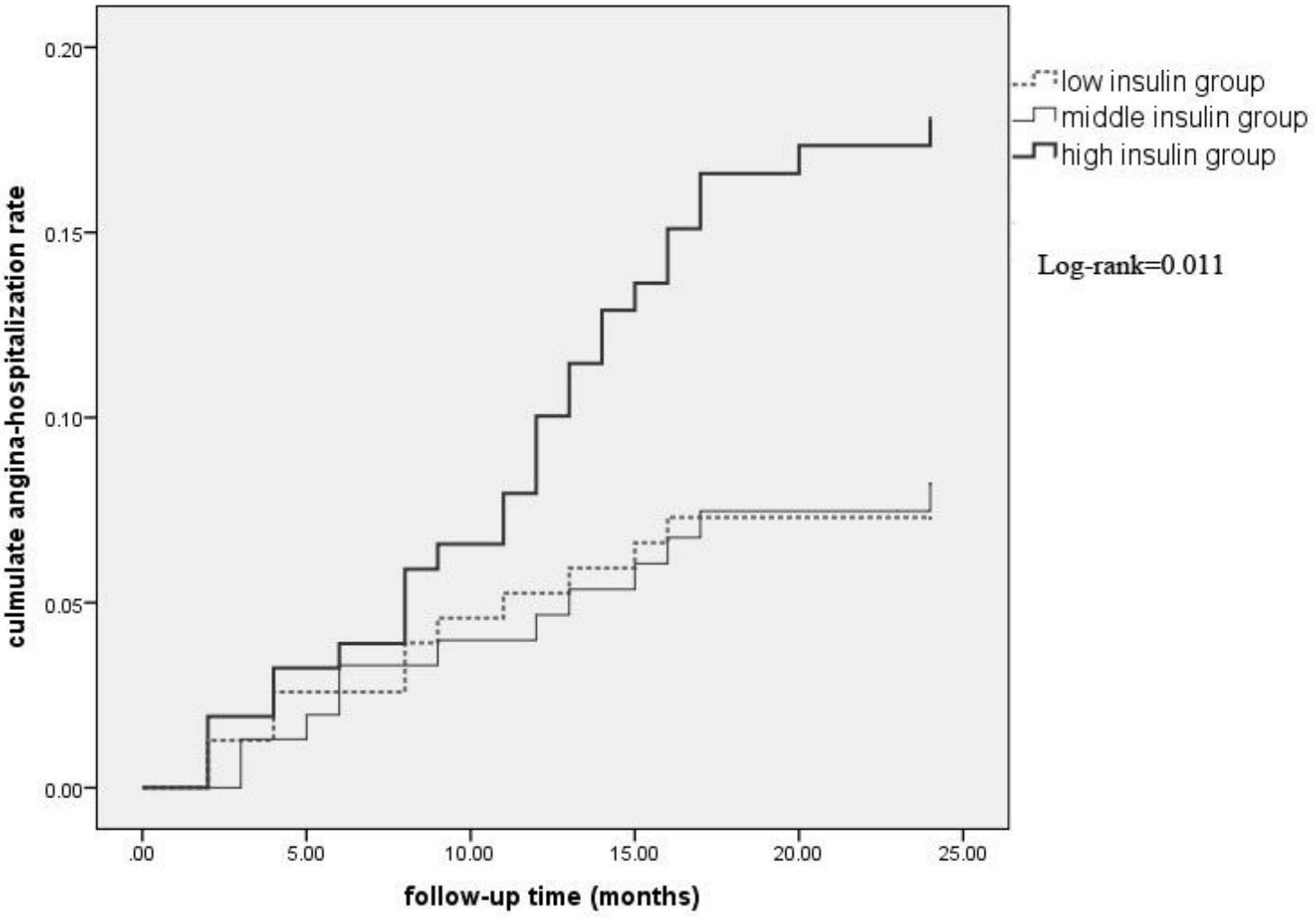

Figure 2

Clinical follow-up was completed in all survival patients. Kaplan-meier survival analyses showed that the high insulin group had an unfavorable prognosis, with higher rates of MACE and angina hospitalization compared with the other two groups at 24 months (Fig2).