Derivation and Evaluation of the Ischemic Risk Model in High-Risk Chinese Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome

Yanguo Xin, PhD[1,2]; Yinan Zhao, PhD[3]; Xin Chen, MD[4]; Junli Li, PhD[1]; Zhiyue Liu, PhD[1]; Xiaofan Cao, PhD[2]; Yingxian Sun, PhD[2]; and Wenyu Hu, PhD[2]

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China; [2]Department of Cardiology, The First Affiliated Hospital, China Medical University, Shenyang, China; [3]Department of Neurology, The First Affiliated Hospital, China Medical University, Shenyang, China; and [4]Department of Cardiology, Fuling Central Hospital, Chongqing, China

ABSTRACT

Purpose: Coronary artery disease is the top cause of death among the Chinese population. With the establishment of a Chinese prediction model, it is urgent to assess factors related to the prognosis of patients with acute coronary syndrome at extremely high risk.

Methods: In this retrospective study, we enrolled 601 patients assessed as being of extremely high risk, according to specific criteria from the China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk) project, and investigated various clinical parameters using Cox multivariate analysis to establish a risk nomogram. C-index and calibration curves were involved to assess the internal identification. By using the all-cause death risk model, we stratified patients by risk level and compared the effects of clopidogrel and ticagrelor on end points.

Findings: We identified several factors, including body mass index, angiopathy, smoking status, β-blocker usage, history of myocardial infarction, total number of stents, and usage of antiplatelet agents, related to ischemic end points, all-cause death, cardiovascular events, and cardiac death. A C-index of >0.7 and the calibration curve demonstrated good concordance. In a subsequent analysis, we used the all-cause death model to stratify patients by risk level, and compared the effects of clopidogrel and ticagrelor. In the subgroup with a 2-year death rate of >50%, ticagrelor showed a positive effect ($P = 0.045$), but in the subgroup with a 2-year death rate of <50%, the difference between clopidogrel and ticagrelor was not significant. Considering the duration of effect of antiplatelet agents, we also compared these 2 agents at 1-year follow up, with ticagrelor showing no advantage.

Implications: We determined the probability of ischemic risk in patients at extremely high ischemic risk and developed new risk models for this specific group. Ticagrelor, compared with clopidogrel, may improve the prognosis of patients at high risk for death after 2 years. (*Clin Ther*. 2019;41:754–765)

Key words: Chinese, clopidogrel, coronary artery disease, extremely high risk, prediction, ticagrelor.

INTRODUCTION

During the past few decades, stroke and ischemic heart disease have risen to the top 2 causes of years of life lost in China. Several tools for cardiovascular disease (CVD) risk evaluation have been published, aiming to guide public health and clinical practice. Well-known examples are the Framingham general CVD equations in the United States,[1] the Systematic Coronary Risk Evaluation

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model in Europe,[2] QRISK in the United Kingdom,[3] and Pooled Cohort Equations for Atherosclerotic CVD (ASCVD) reported in the guideline from the American College of Cardiology and the American Heart Association.[4] However, it is now widely recognized that the risk for CVD is closely related to lifestyle, race, and the living environment. For example, there is a great gap in the dietary habits between Asians and whites that will derive different end points of CVD. The equations mentioned above were all derived from Western samples; however, a rapidly increasing per capita income, an aging population, westernization of lifestyle, and longer life spans have led to dramatic changes in CVD risk patterns in China during the past decade. We are in urgent need of a predictive ASCVD risk model for use in the Chinese population that can help clinicians to both identify patients who are at high risk and provide them proper treatment by more accurate risk estimation.[5]

Current practice guidelines recommend dual antiplatelet treatment with aspirin and clopidogrel or ticagrelor. Despite the fast development of interventional technology, there is still a relatively high prevalence of major adverse cardiovascular and cerebrovascular events (MACCE), such as cardiac death and the need for restenosis. Therefore, in this retrospective study, we aimed to (1) elucidate the underlying risk factors attributing to the ischemic end points in high-risk patients undergoing percutaneous coronary intervention (PCI) and (2) establish validate the risk models. Furthermore, we identified optional treatment strategies for patients by risk stratification.

PATIENTS AND METHODS

Study Design and Patients

We retrospectively collected data from patients with acute coronary syndrome (ACS) admitted to the First Affiliated Hospital of China Medical University (Shenyang, China) for PCI between 2015 and 2016. Eligible patients were assessed for ischemic risk according to the China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk) project.[5] Those evaluated as *extremely high risk* (predicted 10-year ASCVD risk of >10%) attracted our interests. The exclusion criteria included a history of surgical procedure within the preceding year, hematologic disorder, concurrent therapy with a strong cytochrome P-450 3A4 inhibitor or inducer, and pregnancy. We recorded patients' baseline clinical characteristics and risk factors, including smoking status; the presence of dyslipidemia, hypertension, and/or diabetes; and a history of myocardial infarction (MI) and/or angiopathy (defined as stroke, transient ischemic attack, or peripheral vascular disease).

Of 640 patients assessed as extremely high risk and enrolled, 39 were lost to follow-up and 601 were included in the final study population. Of these, 286 patients received ticagrelor, at a loading dose of 180 mg followed by a maintenance dose of 90 mg BID; 316 received clopidogrel at a loading dose of 300 mg followed by a dose of 75 mg daily. All patients received aspirin at a dose of 100 mg daily unless they could not tolerate the drug. In those who had not previously been receiving aspirin, a loading dose of 300 mg was preferred. We collected the detailed medical information of all participants, including basic characteristics, PCI procedural information, and the occurrence of end points during follow-up. All patients' written informed consent and the research protocol were approved by the ethics committee at the First Affiliated Hospital China Medical University.

End Points

The efficacy end point was the prevalence of *MACCE*, defined as a composite of CVD-related death, nonfatal MI, nonfatal stroke, in-stent thrombosis, and/or the need for target vessel revascularization during follow-up. *CVD-related death* was defined as death related to cardiac causes or stroke. *MI* was defined as either the development of new pathologic Q wave in at least 2 contiguous leads or in the absence of pathologic Q waves, an elevation in cardiac biomarkers levels to more than twice the upper limit of normal and unrelated to either PCI with stent or coronary artery bypass grafting.[6] *Stroke* was defined as permanent focal neurologic dysfunction caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death. Evaluation for in-stent thrombosis was performed according to the Academic Research Consortium criteria[7]; we adopted definite and probable in-stent thrombosis in this study. *Target vessel revascularization* was

Table I. Baseline characteristics of the study sample

Characteristics	Clopidogrel (n=286)	Ticagrelor (n=315)	*P* value
Age (yr)	65.62 (8.78)	66.31 (8.96)	0.318
Age ≥ 75yr-no/total no. (%)	34 (11.9)	50 (15.9)	0.159
Male sex-no/total no. (%)	134 (46.9)	148 (47)	0.974
BMI	25.65 (2.61)	25.30 (2.61)	0.813
Cardiovascular risk factors			
Hypertension (%)	152 (53.1)	175 (55.6)	0.554
Diabetes mellitus (%)	132 (46.2)	154 (53.8)	0.066
Dyslipidemia (%)	115 (40.2)	143 (45.4)	0.199
Smoker (%)	155 (54.2)	173 (54.9)	0.859
Previous MI (%)	47 (16.4)	66 (21.0)	0.157
Previous vascular disease (%)	73 (25.5)	87 (27.6)	0.562
Physical findings			
Heart rate	80.15 (15.26)	79.76 (15.69)	0.526
Systolic blood pressure	121.53 (18.05)	120.71 (17.94)	0.755
Diastolic blood pressure	71.32 (42.95)	68.77 (9.69)	0.301
Killip classification (%)			0.097
	211 (67.0)	183 (64.0)	
	63 (20.0)	71 (24.8)	
	36 (11.4)	32 (11.2)	
	5 (1.6)	0 (0.0)	
Laboratory vales			
Hct	0.343 (0.051)	0.344 (0.047)	0.128
Hemoglobulin	147.70 (27.13)	136.17 (28.73)	0.548
PLT	197.83 (50.7)	189.51 (43.10)	0.800
eGFR	105.84 (28.51)	105.59 (28.77)	0.395
Medical history			
ACEI/ARB (%)	220 (76.9)	243 (77.1)	0.949
β-blockers (%)	199 (69.9)	226 (71.7)	0.560
Lipid-lowering agent (%)	269 (94.1)	281 (89.2)	0.033
Tirofiban (%)	187 (65.4)	205 (65.1)	0.937
LMWH (%)	187 (65.4)	250 (79.4)	<0.001
PPI	234 (81.8)	234 (74.3)	0.030
PCI indication			0.319
STEMI (%)	155 (54.2)	181 (57.5)	
Non-STEMI (%)	64 (22.4)	55 (17.5)	
Unstable Angina (%)	67 (23.4)	79 (25.1)	
Total No. of stents	1.65 (0.65)	1.75 (0.69)	0.962
TVD(%)	59 (20.6)	73 (23.2)	0.452
LM involved	52(18.2)	81 (25.7)	0.026
Radial artery access	254 (88.8)	269 (85.4)	0.214

BMI = Body Mass Index; MI = Myocardial Infarction; Hct = haematocrit; PLT = platelet; eGFR = evaluated glomerular filtration rate; ACEI = Angiotensin-Converting Enzyme Inhibitors; ARB = angiotensin receptor blocker; LMWH = low molecular weight heparin; PCI = Percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-Segment elevation myocardial infarction; TVD = triple vessel disease; LM = left main artery.

defined as re-intervention driven by any lesion located in a stented vessel, with the indication for revascularization being based on angina symptoms and/or significant angiographic stenosis (>50% diameter).

Follow-Up

Patients were followed up by phone call and a questionnaire investigation at 6, 12, and 24 months after discharge. Medication adherence and the presence of cardiovascular events were investigated.

Statistical Analysis

Categorical data are presented as frequencies, and continuous variables are expressed using means (SD). We estimated the 2-year cumulative prevalence of MACCE by the Cox regression model. Potential predictors of MACCE were selected at univariate analysis ($P < 0.10$), and the risk nomogram was developed to predict MACCE specifically in patients at extremely high risk. Furthermore, in order to estimate the effects of antiplatelet agents, we compared the end points at 1 year. The nomograms

Table II. Analysis of major adverse cardiovascular and cerebrovascular events: ticagrelor versus clopidogrel.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Antiplatelet agent (ticagrelor vs clopidogrel)	1.30	0.98–1.73	0.060	–	–	–
BMI	1.20	1.13–1.26	<0.001	1.120	1.064–1.180	0.001
Hct	0.042	0.002–0.78	0.034	–	–	–
eGFR	0.99	0.98–0.997	0.039	–	–	–
Hemoglobin	0.984	0.97–0.99	<0.001	–	–	–
Platelets	1.00	0.997–1.003	0.885	–	–	–
Heart rate	1.002	0.993–1.011	0.60	–	–	–
Sex	0.948	0.718–1.251	0.709	–	–	–
Killip classification	1.141	0.952–1.368	0.152	–	–	–
Previous vascular disease	2.718	2.049–3.605	<0.001	2.225	1.651–3.00	<0.001
Diabetes mellitus	1.123	0.851–1.482	0.410	–	–	–
Age	1.004	0.988–1.020	0.571	–	–	–
Diagnosis	1.012	0.858–1.192	0.885	–	–	–
Hypertension	1.302	0.982–1.727	0.066	–	–	–
Smoker	1.702	1.273–2.277	<0.001	1.844	1.366–2.488	<0.001
Previous MI	5.055	3.800–6.726	<0.001	4.180	3.079–6.675	<0.001
Total stents	1.302	1.061–1.599	0.011	–	–	–
No. of lesioned vessels	1.198	1.014–1.415	0.011	–	–	–
Radial artery access	1.328	0.845–2.087	0.218	–	–	–
LM involvement	1.394	1.020–1.905	0.036	–	–	–
GP IIb/IIa inhibitor	0.586	0.443–0.774	<0.001	–	–	–
PPI	1.037	0.742–1.449	0.830	–	–	–
LMWH	0.891	0.637–1.246	0.501	–	–	–
β-Blocker	0.515	0.387–0.683	<0.001	0.557	0.416–0.745	<0.001
ACEI/ARB	0.926	0.671–1.279	0.644	–	–	–

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; GP = glycoprotein; Hct = hematocrit; HR = hazard ratio; LM = left main artery; LMWH = low–molecular weight heparin; MI = myocardial infarction; PPI = proton pump inhibitor.

were assessed using a bootstrap cross-validation method (1000 bootstrap resamples).

We evaluated both discrimination and calibration. The C-index was used to quantify discrimination. The calibration plot was used to assess the predicted probabilities from the model versus the actual probabilities. A difference was considered statistically significant if a 2-sided *P* value was <0.05. Data were analyzed with Stata software version 12.0 and R version 3.4.4 (http://www.r-project.org).

RESULTS

We sequentially enrolled 640 patients diagnosed with ACS undergoing PCI between September 2015 and February 2016. Follow-up ended in April 2018, with a median duration of follow-up of 21.4 (maximum, 24) months. Complete follow-up information was obtained from 93.9% of patients. Table I illustrates the baseline and procedural characteristics of all 601 patients with intact follow-up information, with or without available outcomes data.

We entered the predictors with a *P* value of <0.10 on univariate analysis into the multivariate model according to Cox analysis. To get more specific information about end points, we analyzed total MACCE, all-cause death, cardiac events, and cardiac death separately. With regard to total MACCE, 15 factors from the univariate analysis were used in the subsequent multivariate Cox analysis (Table II). In the multivariate analysis, we found that a history of angiopathy, smoking, MI, and/or β-blocker usage, as well as body mass index (BMI), were associated with patients' prognosis, and we established a nomogram for this risk model (Figure 1A). The prediction model showed a C-index of 0.764. In addition, the calibration curve demonstrated good concordance between the predicted and actual outcomes (Figure 2A), indicating that our score model could predict the MACCE rate effectively. Similar to

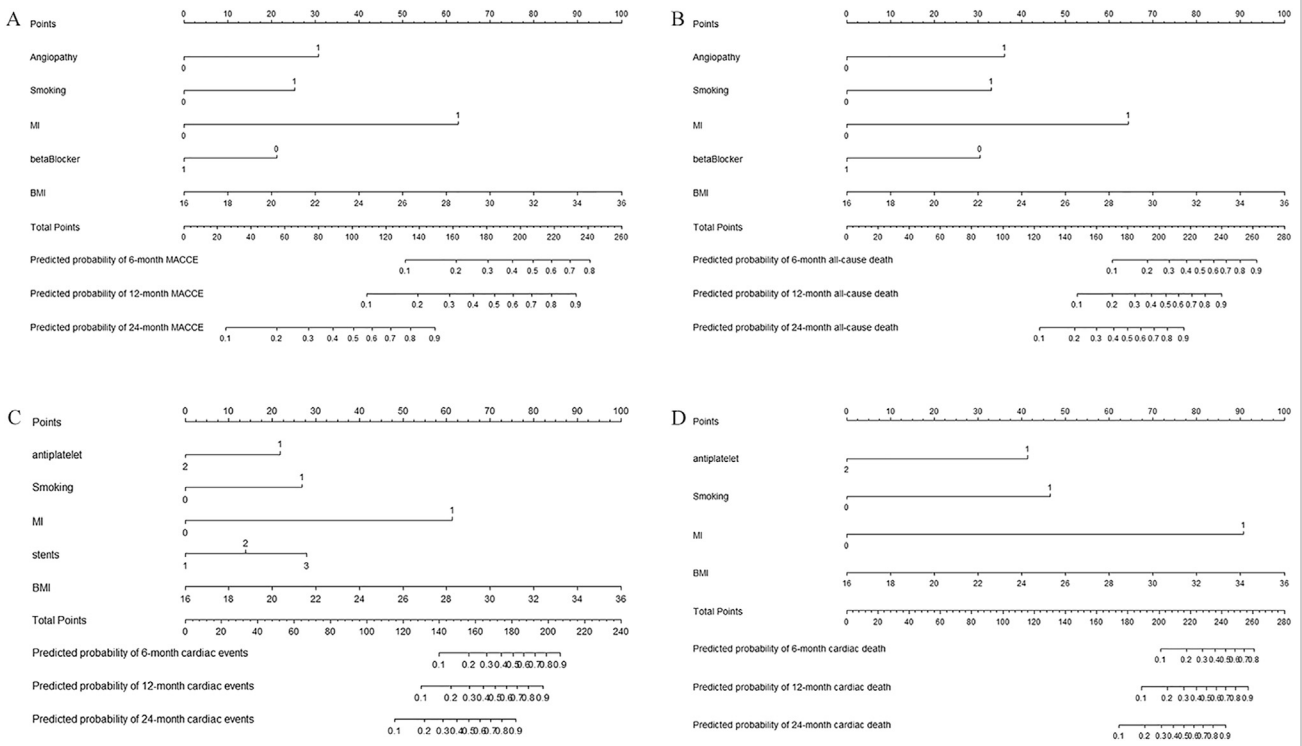

Figure 1. Nomograms of end points. A, Total major adverse cardiovascular and cerebrovascular events (MACCE); B, all-cause death; C, cardiac events; D, cardiac death. BMI = body mass index; MI = myocardial infarction.

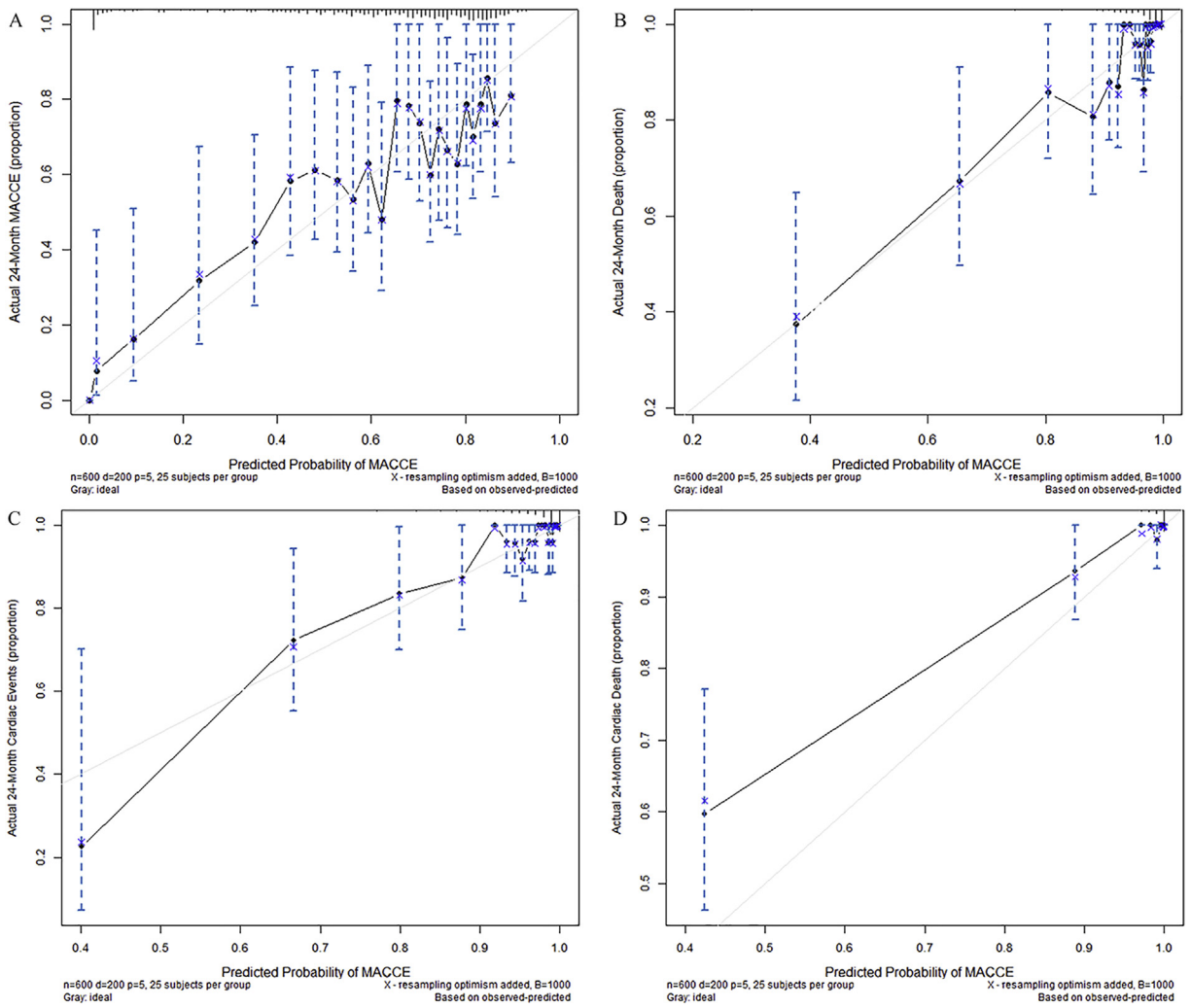

Figure 2. Calibration curves of established models. A, Total major adverse cardiovascular and cerebrovascular events (MACCE); B, all-cause death; C, cardiac events; D, cardiac death.

MACCE, a history of angiopathy, smoking, MI, and/or β-blocker usage, as well as BMI, were 5 factors that influenced patients' all-cause death (Table III). The C-index of the risk model was 0.9228, and the calibration curve demonstrated good concordance between the predicted and actual outcomes (Figure 2B). In the evaluation of cardiac events, 5 factors, including the number of stents implanted; BMI; and history of MI, smoking, and/or use of antiplatelet agents, showed effects on the prognosis of patients with ACS (Table IV). The evaluation of the internal verification of the model (Figure 1C) is shown in Figure 2C. With regard to cardiac death in patients diagnosed with ACS, use of antiplatelet agents, BMI, and a history of smoking and/or MI were 4 factors influencing prognosis (Table V).

After the identification of the risk factors for prognosis, we evaluated the risk for prognosis and stratified the patients according to the all-cause death nomogram; then, we compared the effects of ticagrelor and clopidogrel by risk for death at 2 years. In the subgroups with 2-year death rates of <10% and 10%−30%, there were no significant effects with clopidogrel versus ticagrelor ($P = 0.446$

Table III. Analysis of all-cause death: ticagrelor versus clopidogrel.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Antiplatelet agent (ticagrelor vs clopidogrel)	0.677	0.399−1.150	0.149	—	—	—
BMI	1.432	1.311−1.564	<0.001	1.169	1.067−1.280	0.001
Hct	0.014	0.000−3.544	<0.001	—	—	—
eGFR	0.972	0.959−0.984	<0.001	—	—	—
Hemoglobin	0.959	0.948−0.971	<0.001	—	—	—
Platelet	1.00	0.995−1.006	0.811	—	—	—
Heart rate	1.005	0.989−1.021	0.530	—	—	—
Sex	1.085	1.179−3.686	0.011	—	—	—
Killip classification	1.418	1.037−1.939	0.028	—	—	—
Previous vascular disease	6.902	3.934−12.106	<0.001	3.853	2.038−7.287	<0.001
Diabetes mellitus	1.501	0.884−2.548	0.132	—	—	—
Age	1.024	0.992−1.056	0.133	—	—	—
Diagnosis	0.949	0.692−1.301	0.747	—	—	—
Hypertension	1.408	0.820−2.420	0.214	—	—	—
Smoker	3.633	1.879−7.025	<0.001	3.395	2.038−7.287	<0.001
Previous MI	16.727	9.232−30.30	<0.001	8.948	4.617−17.342	<0.001
Total stents	1.870	1.302−2.687	<0.001	—	—	—
No. of lesioned vessels	1.840	1.360−2.488	<0.001	—	—	—
Radial artery access	1.542	0.615−3.864	0.355	—	—	—
LM involvement	1.740	0.993−3.049	0.052	—	—	—
GP IIb/IIa	0.487	0.288−0.823	0.007	—	—	—
PPI	1.300	0.656−2.577	0.450	—	—	—
LMWH	0.985	0.520−1.865	0.964	—	—	—
β-Blocker	0.224	0.130−0.385	<0.001	0.298	0.167−0.533	<0.001
ACEI/ARB	0.953	0.512−1.772	0.879	—	—	—

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; GP = glycoprotein; Hct = hematocrit; HR = hazard ratio; LM = left main artery; LMWH = low−molecular weight heparin; MI = myocardial infarction; PPI = proton pump inhibitor.

and $P = 0.384$, respectively), while in the subgroup with a 2-year death rate of 30%−50%, the rate of all-cause death was significantly decreased with ticagrelor (hazard ratio = 0.157; 95% CI, 0.025−0.962; $P = 0.045$). In the subgroup with a 2-year death rate of >50%, ticagrelor was not associated with a decrease in the all-cause death rate compared with clopidogrel ($P = 0.217$) (Figure 3). To further analyze the end points, we used a competing risk model to determine whether ticagrelor could decrease the risk for cardiac death, by comparing the rates of noncardiac death in patients at high risk for death. Ticagrelor was associated with a decreased risk for cardiac death in both predictive and observational models of competing risks regression analysis (subdistribution hazard ratio = 0.348; 95%CI, 0.124−0.978; $P = 0.045$) (Figures 3 and 4).

DISCUSSION

Our project enrolled extremely high−risk patients with ACS and developed and validated a risk model for providing more information to physicians during the planning of therapeutic strategies. The equations had

excellent performance of MACCE prediction, with good internal consistency. Meanwhile, we compared the effects of clopidogrel and ticagrelor. Our results demonstrated that ticagrelor may decrease the prevalence of cardiac death among patients with a 2-year risk for all-cause-death of >50%, but because the *P* value was near 0.05, likely due to the relatively small sample size, this tendency could not be obviously demonstrated. Another reason for this situation may have been that we screened extremely high−risk patients according to criteria from the China-PAR trial and further stratified risk in patients with ACS and found the optimal agents for different patients.

ACS, as an acute manifestation of coronary heart disease, results in substantial morbidity and mortality in China. Currently, about 230 million Chinese individuals are living with cardiovascular disease.[8] However, several recently published studies have shown low utilization rates of guideline-recommended therapies in patients with ACS in China.[9,10] Dual antiplatelet therapy (DAPT) with

Table IV. Analysis of cardiac events: ticagrelor versus clopidogrel.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Antiplatelet agent (ticagrelor vs clopidogrel)	0.603	0.352−1.035	0.066	0.342	0.192−0.612	<0.001
BMI	1.426	1.304−1.559	<0.001	1.266	1.155−1.388	<0.001
Hct	0.0006	0.000−0.180	0.010	—	—	—
eGFR	0.982	0.971−0.994	0.005	—	—	—
Hemoglobin	0.966	0.955−0.978	<0.001	—	—	—
Platelets	1.001	0.996−1.006	0.575	—	—	—
Heart rate	1.004	0.988−1.021	0.583	—	—	—
Sex	1.256	0.735−2.147	0.403	—	—	—
Killip classification	1.221	0.874−1.707	0.240	—	—	—
Previous vascular disease	5.576	3.215−9.672	<0.001	—	—	—
Diabetes mellitus	1.561	0.913−2.668	0.103	—	—	—
Age	1.027	0.995−1.060	0.098	—	—	—
Diagnosis	0.943	0.685−1.298	0.719	—	—	—
Hypertension	1.479	0.853−2.562	0.162	—	—	—
Smoker	2.836	1.522−5.284	0.001	3.624	1.865−7.042	<0.001
Previous MI	18.912	10.118−35.348	<0.001	15.701	8.082−30.505	<0.001
Total stents	2.041	1.422−2.930	<0.001	2.077	1.290−3.344	0.003
No. of lesioned vessels	1.627	1.201−2.205	0.001	—	—	—
Radial artery access	1.507	0.601−3.781	0.381	—	—	—
LM involvement	1.923	1.103−3.353	0.021	—	—	—
GP IIb/IIa	0.240	0.136−0.422	<0.001	—	—	—
PPI	0.690	0.385−1.235	0.211	—	—	—
LMWH	1.574	0.744−3.332	0.235	—	—	—
β-Blocker	0.365	0.215−0.620	<0.001	—	—	—
ACEI/ARB	0.706	0.394−1.264	0.242	—	—	—

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; GP = glycoprotein; Hct = hematocrit; HR = hazard ratio; LM = left main artery; LMWH = low−molecular weight heparin; MI = myocardial infarction; PPI = proton pump inhibitor.

aspirin and a $P2Y_{12}$ receptor inhibitor represents the cornerstone of ACS management.[11–13] The PLATO (Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes) trial had proved the efficacy and tolerability of ticagrelor in ACS, but it enrolled only about 587 ACS patients of Chinese ethnicity (3.1% of 18,758 enrolled patients).[14] Compared with the white population, Chinese patients tend to have a lower BMI and a higher prevalence of renal failure, both of which are associated with more bleeding complications,[15–17] and different risk profiles for thrombophilia and bleeding.[18] In addition, despite multiple established prediction models, there are huge gaps in the epidemics of and risk factors for CVD between Western and Chinese patients. With the publication of the China-PAR project,[5] we provided an effective tool to assess the risk in Chinese patients. Among ACS patients at extremely high risk, several factors were associated with MACCE in our models, and BMI is one of them. Previous trials have identified the relationship between bleeding and BMI,[16,19] but few trials have focused on MACCE,

Table V. Analysis of cardiac death: ticagrelor versus clopidogrel.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Antiplatelet agent (ticagrelor vs clopidogrel)	0.316	0.133–0.748	0.008	0.165	0.067–0.405	<0.001
BMI	1.418	1.250–1.610	<0.001	1.242	1.081–1.427	0.002
Hct	0.000	0.000–0.153	0.015	—	—	—
eGFR	0.980	0.963–0.998	0.032	—	—	—
Hemoglobin	0.962	0.946–0.979	<0.001	—	—	—
Platelets	0.999	0.991–1.007	0.915	—	—	—
Heart rate	1.009	0.986–1.032	0.436	—	—	—
Sex	2.148	0.940–4.909	0.069	—	—	—
Killip classification	1.616	1.050–2.487	0.029	—	—	—
Previous vascular disease	5.369	2.454–11.743	<0.001	—	—	—
Diabetes mellitus	2.249	1.010–5.008	0.047	—	—	—
Age	1.024	0.979–1.071	0.290	—	—	—
Diagnosis	1.118	0.722–1.732	0.615	—	—	—
Hypertension	2.000	0875–4.570	0.099	—	—	—
Smoker	5.047	1.745–14.597	0.002	7.641	2.510–23.255	<0.001
Previous MI	46.695	14.016–155.56	<0.001	57.520	16.531–200.1	<0.001
Total stents	2.246	1.349–3.740	0.001	—	—	—
No. of lesioned vessels	1.470	0.952–2.271	0.081	—	—	—
Radial artery access	1.881	0.445–7.944	0.389	—	—	—
LM involvement	2.503	1.161–5.395	0.019	—	—	—
GP IIb/IIa	0.247	0.110–0.549	<0.001	—	—	—
PPI	1.243	0.470–3.283	0.660	—	—	—
LMWH	1.184	0.448–3.128	0.732	—	—	—
β-Blocker	0.223	0.102–0.488	<0.001	—	—	—
ACEI/ARB	1.009	0.407–2.501	0.983	—	—	—

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; GP = glycoprotein; Hct = hematocrit; HR = hazard ratio; LM = left main artery; LMWH = low–molecular weight heparin; MI = myocardial infarction; PPI = proton pump inhibitor.

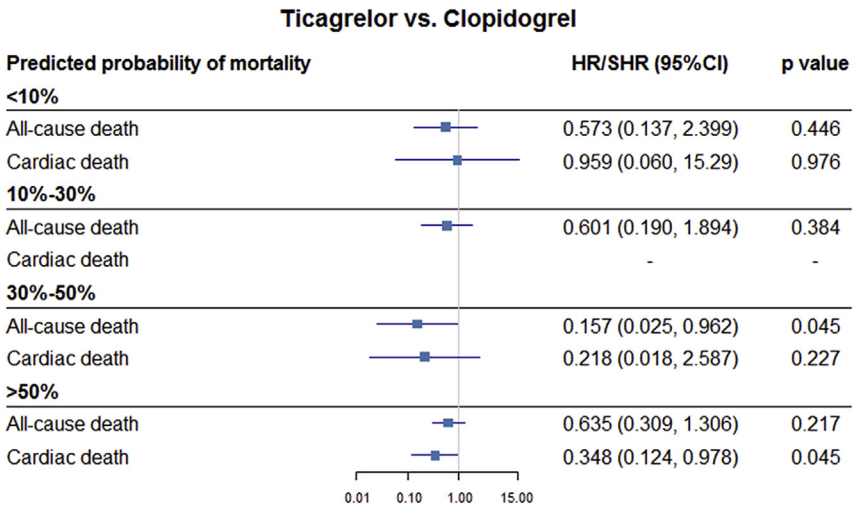

Figure 3. Two-year rates of all-cause death with ticagrelor versus clopidogrel. HR = hazard ratio; SHR = subdistribution hazard ratio.

especially in Asians. Our study concludes that BMI is an important factor during the evaluation of ischemic prognosis in Chinese patients. In fact, the pharmacokinetic properties of antiplatelet agents are related to body size.[20,21] In the future, we will pay more attention to BMI, trying to find optimal antiplatelet therapeutic strategies for patients of different BMI stratifications.

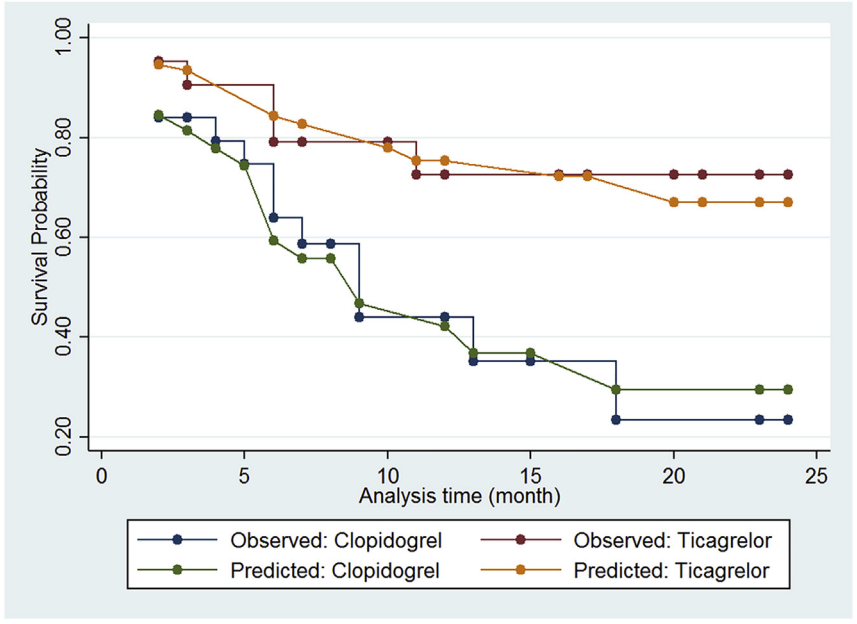

Figure 4. Probability of survival in observed and predicted conditions with ticagrelor versus clopidogrel.

Our project provides physicians the Chinese-specific equations for ischemic risk estimation to make it easy to match the probability of improved end points with the intensity of risk factor lowering. It could help physicians to understand and recognize ACS patients at high ischemic risk and to use appropriate strategies, including the choice of antiplatelet agent.

In the subgroup with a 2-year death rate of >50%, the antiplatelet strategies were not found to have contributed to MACCE or all-cause death. We elucidated the information on these patients and found that the relative high bleeding risk might have contributed to the results.

With regard to the course of antiplatelet treatment, in this trial, all patients enrolled received DAPT for 1 year (aspirin with clopidogrel or ticagrelor at standard dosages) and continued to receive aspirin after 1 year. However, in the second year, patients received only aspirin, which would have introduced a bias with regard to MACCE when we compared clopidogrel and ticagrelor. Considering this situation, we also investigated the effects of these 2 agents at 1 year. The results showed no significant difference in all-cause death between clopidogrel and ticagrelor at 1-year follow-up at any risk level ($P = 0.124$, 0.152, 0.394, and 0.805 at <10%, 10%−30%, 30%−50%, and >50% death rates, respectively). This finding might be explained by the limited number of enrolled patients and the intermediate-term follow-up. We need to increase enrolled patients to observe whether ticagrelor has a long-term effect on prognosis, and the efficiency of ticagrelor in patients during the DAPT phase.

Limitations

Several limitations of our modeling should be addressed. First, the outcomes events in the present research encompassed only the hard end points of ASCVD, while some atherosclerosis-related events, such as angina pectoris and intermittent claudication, were not included. Second, the sample size of patients involved in this study was relatively small, which may have introduced selective bias and statistically unapparent differences, and reduced generalizable applicability. Finally, we were unable to conduct independent external validation to confirm efficacy or identify a possible additional index that might strengthen the mathematical basis of prediction.

CONCLUSIONS

We determined the probability of MACCE in patients with ACS and a predicted 10-year ASCVD risk of >10% who underwent PCI; we developed new nomograms that will help physicians to choose optimal treatment strategies. According to the findings from our study, ticagrelor provided a benefit to patients with a high 2-year risk for death by reducing MACCE, while among patients with a relatively low expected mortality risk, clopidogrel shared similar therapeutic effects.

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All of the authors contributed to the design of the study and the writing of the manuscript. Yanguo Xin conceived and designed the study, analyzed the data, and wrote the manuscript. Yinan Zhao conceived and designed the study. Xin Chen participated in data collection. Junli Li participated in data collection. Zhiyue Liu participated in data collection. Xiaofan Cao participated in data collection. Yingxian Sun conceived and designed the study. Wenyu Hu conceived and designed the study, analyzed the data, and wrote the manuscript. All of the authors read and approved the final manuscript.

The study design, collection of the data, analysis, interpretation of the data, writing the manuscript and decision to publish was the sole responsibility of the authors and independent of the funders.

CONFLICTS OF INTERESTS

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Address correspondence to: Wenyu Hu, PhD, Department of Cardiology, The First Affiliated Hospital, China Medical University, Shenyang, Liaoning Province, 110001, China. E-mail: huwen0320@sohu.com