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ORIGINAL RESEARCH

In-Hospital Outcomes of Dual Loading Antiplatelet Therapy in Patients 75 Years and Older With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: Findings From the CCC-ACS (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) Project

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***Background*—**Elderly patients with acute coronary syndrome (ACS) are at high risk for ischemic and bleeding events. This study aimed to evaluate the clinical effectiveness and safety of dual loading antiplatelet therapy for patients 75 years and older undergoing percutaneous coronary intervention for ACS.

***Methods and Results*—**The Improving Care for Cardiovascular Disease in China-ACS project was a collaborative study of the American Heart Association and Chinese Society of Cardiology. A total of 5887 patients 75 years and older with ACS who had percutaneous coronary intervention and received dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitors (clopidogrel or ticagrelor) between November 2014 and June 2017 were enrolled. The primary effectiveness and safety outcomes were in-hospital major adverse cardiovascular events and major bleeding. Hazard ratios (HRs) of in-hospital outcomes with different loading statuses of antiplatelet therapy were estimated using Cox proportional hazard models with multivariate adjustment. A propensity score–matched analysis was also conducted. Compared with patients receiving a dual nonloading dose, patients taking a dual loading dose had increased risks of both major adverse cardiovascular events (HR, 1.66, 95% confidence interval, 1.13–2.44; [P=0.010]) and major bleeding (HR, 2.34, 95% confidence interval, 1.75–3.13; [P<0.001]). Among 3284 propensity score–matched patients, a dual loading dose was associated with a 1.36-fold risk of major adverse cardiovascular events (HR, 1.36; 95% confidence interval, 0.88–2.11 [P=0.168]) and a 2.08-fold risk of major bleeding (HR, 2.08; 95% confidence interval, 1.47–2.93 [P<0.001]).

***Conclusions*—**A dual loading dose of antiplatelet therapy was associated with increased major bleeding risk but not with decreased major adverse cardiovascular events risk among patients 75 years and older undergoing percutaneous coronary intervention for ACS in China.

***Clinical Trial Registration*—**URL: http://www.ClinicalTrials.gov. Unique identifier: NCT02306616. **(*J Am Heart Assoc*. 2018;7: e008100. DOI: 10.1161/JAHA.117.008100.)**

Key Words: acute coronary syndrome • antiplatelet therapy • elderly • loading dose • percutaneous coronary intervention

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Accompanying Data S1, Tables S1 through S4, Figures S1 through S5, and Appendix S1 are available at http://jaha.ahajournals.org/content/7/7/e008100/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of CCC-ACS Investigators are given in Appendix S1.

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Clinical Perspective

What Is New?

- This is the first registry study with a relatively large sample size focused on the effectiveness and safety of a dual loading versus nonloading dose of aspirin and $P2Y_{12}$ receptor inhibitor in patients 75 years and older with acute coronary syndromes undergoing percutaneous coronary intervention.
- Our study shows that a dual loading dose of antiplatelet therapy is not associated with reduced risk of in-hospital major adverse cardiovascular events, but with significantly increased risk of major bleeding among patients 75 years and older with acute coronary syndromes undergoing percutaneous coronary intervention in China.

What Are the Clinical Implications?

- There is a considerable proportion of patients older than 75 years with acute coronary syndromes seen in clinical practice, but there is still a relative lack of evidence on treatment strategies for these patients.
- The potential risks and benefits regarding use of a dual loading dose of aspirin and $P2Y_{12}$ receptor inhibitors should be carefully considered in patients 75 years and older with acute coronary syndromes undergoing percutaneous coronary intervention.

Over the past 2 decades, oral dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor has become the cornerstone for treating patients with acute coronary syndrome (ACS).[1] For patients with ACS undergoing percutaneous coronary intervention (PCI), a loading dose of dual antiplatelet therapy is strongly recommended as early as possible or at the time of PCI by the latest guidelines.[2–5]

However, the elderly, especially those 75 years and older, who account for a large proportion of patients with ACS in clinical practice, were underrepresented, or even excluded, in randomized trials that provided evidence for guidelines.[6] These patients are generally more vulnerable to the adverse effects of a loading dose of antithrombotic drugs. One of the most noteworthy complications is bleeding, which is associated with prolonged hospitalization and increased mortality.[7–9] However, recommendations in the guidelines are the same for all ages, except for those receiving thrombolytic therapy.[2,5]

An increasing number of researches have been performed focusing on antiplatelet therapy for elderly patients, such as the the POPular AGE (Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-Risk Elderly) study and the Elderly-ACS 2 Study.[10,11] However, there are limited data regarding the effectiveness and safety of a dual loading dose of antiplatelet therapy in patients 75 years and older with ACS undergoing PCI.

In this study, we aimed to evaluate whether receiving a dual loading dose of antiplatelet agents is appropriate for patients 75 years and older with ACS who underwent PCI during hospitalization.

Methods

For the concern about intellectual property and patient privacy, the data, analytic methods, and study materials of this study will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

The CCC-ACS (Improving Care for Cardiovascular Disease in China-ACS) project is a nationwide registry and quality improvement study with an ongoing database focusing on quality of ACS care. This study was launched in 2014 as a collaborative initiative of the American Heart Association and Chinese Society of Cardiology. Details of the design and methodology of the CCC-ACS project have been published.[12] A standard web-based data collection platform (Oracle Clinical Remote Data Capture, Oracle) was used. Trained data abstractors in the participating hospitals reported the required data, which they abstracted from the patients' medical records. Eligible patients were consecutively reported to the CCC-ACS database for each month before the middle of the following month. Third-party clinical research associates were hired to perform quality audits to ensure that cases were reported consecutively rather than selectively. Additionally, ≈5% of reported cases from every participating center were randomly selected every 3 months. Selected data were then compared with the original medical records to ensure accuracy and completeness. According to the quality audit reports, the data in this study were appropriately reported with a low incidence of missing data or error. The quality audit reports were also fed back to each center regularly to ensure data quality.

Study Population

On the basis of principal discharge diagnosis, 63 641 patients with ACS from 145 hospitals were registered from November 1, 2014, to June 30, 2017. Of these, 6384 patients 75 years and older who received a known dose of both aspirin and $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) without switching drugs within 24 hours of first medical contact and received PCI during hospitalization were included in this

study. Of these 6384 patients enrolled in our study, 497 patients were excluded, including 31 patients with treatment of warfarin within 2 weeks before admission, 91 patients with fibrinolytic therapy, 59 patients who died within 24 hours of admission, and 316 patients lacking important clinical data (Figure 1, Data S1). Institutional review board approval was granted for this research by the ethics committee of Beijing Anzhen Hospital, Capital Medical University. No informed consent was required.

Dual Antiplatelet Therapy Within 24 Hours of First Medical Contact

According to the type and dose of antiplatelet therapy received within 24 hours of first medical contact, patients were divided into 4 groups as follows: loading with neither aspirin nor $P2Y_{12}$ receptor inhibitor (nonloading group); only loading with aspirin, but not with $P2Y_{12}$ receptor inhibitor (only aspirin loading group); only loading with $P2Y_{12}$ receptor inhibitor, but not with aspirin (only $P2Y_{12}$ receptor inhibitor loading group); and loading with both aspirin and $P2Y_{12}$ receptor inhibitor (dual loading group). The loading dose of aspirin was defined as ≥150 mg and the loading dose of $P2Y_{12}$ receptor inhibitor was defined as ≥300 mg of clopidogrel or ≥180 mg of ticagrelor. There were 1997 patients (96.6% of patients with aspirin loading) taking a 300-mg dose of aspirin and 1407 patients (84.0% of patients with clopidogrel loading) taking a 300-mg dose of clopidogrel and 744 patients (99.7% of patients with ticagrelor loading) taking a 180-mg dose of ticagrelor. The nonloading dose of aspirin was <150 mg and the nonloading dose of $P2Y_{12}$ receptor inhibitor was defined as 75 to 150 mg of clopidogrel or 90 to 135 mg of ticagrelor. There were 3796 patients (99.4% of patients with aspirin nonloading) taking a 100-mg dose of aspirin. In addition, there were 3004 patients (94.4% of patients with clopidogrel nonloading) taking a 75-mg dose

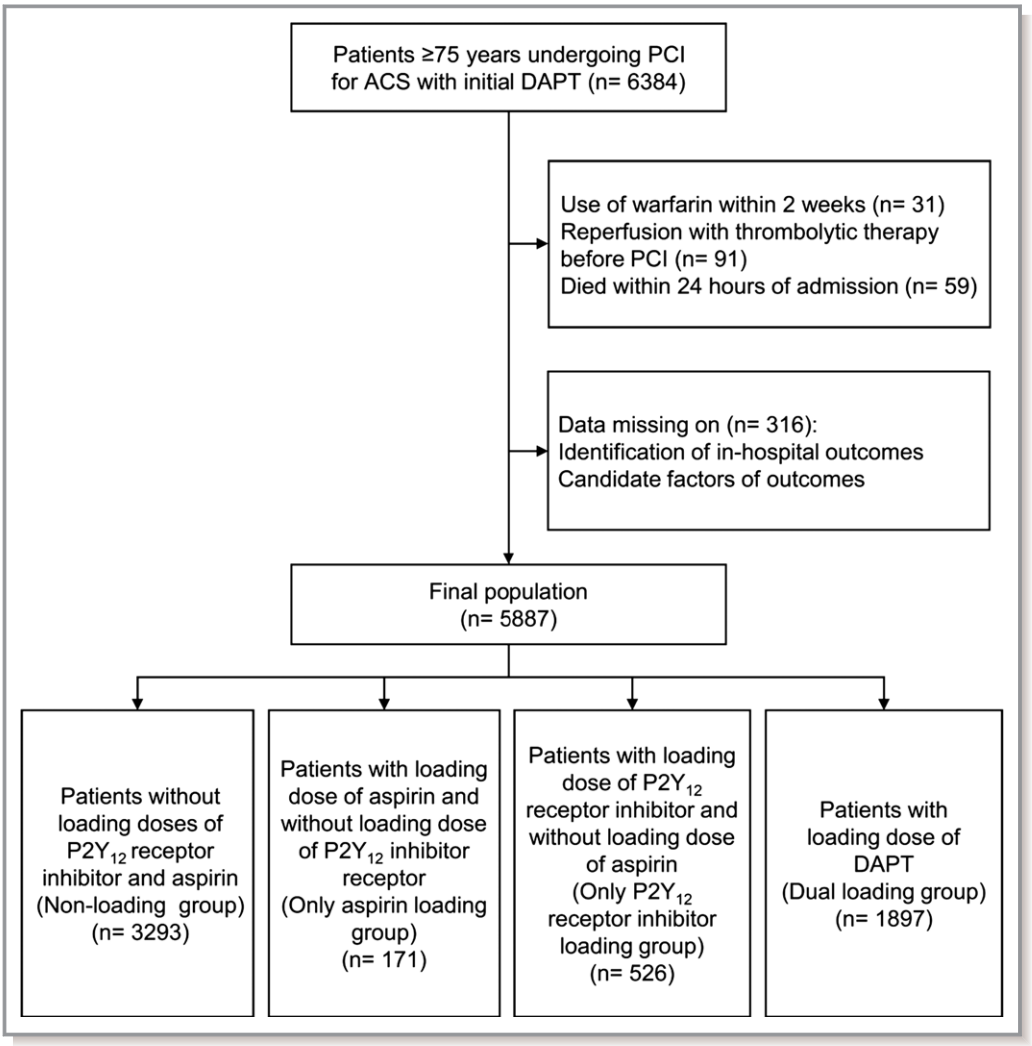

Figure 1. Flow diagram of selection of the study population. ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

of clopidogrel and 283 patients (97.6% of patients with ticagrelor nonloading) taking a 90-mg dose of ticagrelor. The detailed doses of each oral antiplatelet drug are provided in supplemental files.

In-Hospital Outcomes

In this study, the primary effectiveness outcome was major adverse cardiovascular event (MACE), including cardiac death, myocardial infarction (MI), stent thrombosis, and ischemic stroke during hospitalization. The secondary effectiveness outcome was in-hospital all-cause death. The primary safety outcome in our study was in-hospital major bleeding, including intracranial bleeding, retroperitoneal bleeding, decline in hemoglobin levels ≥4 g/dL during hospitalization, transfusion with overt bleeding, or bleeding requiring surgical intervention.[13] We also examined all bleeding events as our secondary safety outcome, including all documented bleeding (intracranial bleeding, retroperitoneal bleeding, access-site bleeding, gastrointestinal bleeding, skin or mucosa bleeding, and other sites bleeding) or a decline in hemoglobin levels ≥3 g/dL during hospitalization. Minor bleeding was defined as bleeding events excluding major bleeding.

Statistical Analysis

Demographic information, medical history, clinical and procedural characteristics, and in-hospital outcomes of the participants were described by the different loading statuses of antiplatelet therapy (Tables 1 and 2). Continuous variables were shown as mean±SD or median (interquartile range) according to different distributions. Categorical variables were presented as the number (percentage). Differences in various characteristics among the groups were compared using 1-way ANOVA, Kruskal–Wallis test, and chi-square test. The characteristics between the dual loading group and the nonloading group were further compared by *t* test, Wilcoxon test, and chi-square test.

Survival curves of MACE, all-cause death, major bleeding, and all bleeding events were displayed using Kaplan–Meier curves and compared using log-rank tests. Multivariable Cox proportional hazard model was performed to examine the association between different loading statuses and in-hospital outcomes by controlling potentially confounding factors. Candidate adjustment variables included age, sex, previous MI, previous PCI, heart failure history, renal failure history, ischemic stroke history, hemorrhagic stroke history, diabetes mellitus, hypertension, preadmission use of $P2Y_{12}$ receptor inhibitors, preadmission use of aspirin, preadmission use of β-blockers, type of ACS, Killip classes, stent(s) implantation, type of stent(s), access site of PCI, baseline hemoglobin, elevated serum creatinine level, systolic blood pressure, heart rates, type of $P2Y_{12}$ receptor inhibitor used within 24 hours of first medical contact, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, statins, glycoprotein IIb/IIIa inhibitors, and anticoagulant therapy during hospitalization. After forward stepwise selection with entry and exit criteria setting at the P=0.05 and 0.1 level, respectively, the variables listed in Tables 3 and 4 were eventually included in the multivariable Cox proportional hazard model of MACE and major bleeding, respectively. Because the majority of patients were hospitalized for ≈2 weeks, this study only took incidents that occurred within 15 days of admission into account. Therefore, all Kaplan–Meier curves and performed Cox regression were constructed based on a 15-day observation. Hazard ratios (HRs) for different variables and corresponding 95% confidence intervals (CIs) were reported.

As most of the patients received either a dual loading dose of antiplatelet therapy or a dual nonloading dose in clinical practice, we compared the differences of in-hospital outcomes between these 2 groups in a propensity score–matched population to minimize selection bias from the real world. Patients with a dual loading dose were matched 1:1 with patients randomly selected from the dual nonloading group with no replacement, on the basis of the nearest neighbor in terms of Mahalanobis distance with a caliper of 0.02. The propensity score of exposure to a dual loading dose was estimated with a logistic regression model with the variables of age, sex, first medical contact site, participating hospitals, diabetes mellitus, systolic blood pressure, heart rates, Killip classes, type of ACS, preadmission use of $P2Y_{12}$ receptor inhibitors, preadmission use of aspirin, preadmission use of β-blockers, previous MI, previous PCI, heart failure history, renal failure history, ischemic stroke history, hemorrhagic stroke history, and elevated serum creatinine level. The incidence of in-hospital outcomes between the 2 propensity score–matched subsets were compared. As some characteristics were not well comparable between the 2 groups even after the propensity score matching, multivariable Cox proportional hazard model was further performed to compare the risk by adjusting factors, which were eventually included in the whole population by forward stepwise selection.

Subgroup analyses of primary outcomes were then performed based on important characteristics, including age (younger than 80 years or 80 years and older), sex (male or female), type of ACS (ST-segment elevation MI or non–ST-segment elevation ACS), preadmission antiplatelet therapy (no or yes), type of $P2Y_{12}$ receptor inhibitor used within 24 hours of first medical contact (clopidogrel or ticagrelor), hypertension (no or yes), diabetes mellitus (no or yes), Global Registry of Acute Coronary Events score (≥140 or <140), Killip class I (no or yes), and glycoprotein IIb/IIIa inhibitors (no or yes).

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Table 1. Baseline Characteristics

	Unmatched						Propensity Score–Matched		
	Nonloading (n=3293)	Only Aspirin Loading (n=171)	Only $P2Y_{12}$ Receptor Inhibitor Loading (n=526)	Dual Loading (n=1897)	*P* Value of 4 Groups*	*P* Value of Nonloading and Dual Loading Groups†	Nonloading (n=1642)	Dual Loading (n=1642)	*P* Value†
Age, y	79.91±3.66	80.20±3.44	79.96±4.05	80.20±4.02	0.059	0.008	80.06±3.74	80.06±3.92	0.998
Male	2072 (62.9)	107 (62.6)	343 (65.2)	1162 (61.3)	0.371	0.233	1010 (61.5)	1024 (62.4)	0.615
Comorbidity									
Previous MI	314 (9.5)	16 (9.4)	45 (8.6)	96 (5.1)	<0.001	<0.001	81 (4.9)	91 (5.5)	0.433
Previous PCI	395 (12.0)	19 (11.1)	45 (8.6)	113 (6.0)	<0.001	<0.001	105 (6.4)	106 (6.5)	0.943
Previous CABG	22 (0.7)	3 (1.8)	5 (1.0)	3 (0.2)	0.007	0.011	6 (0.4)	3 (0.2)	0.317
Hypertension	2413 (73.3)	116 (67.8)	375 (71.3)	1346 (71.0)	0.157	0.071	1184 (72.1)	1161 (70.7)	0.374
Dyslipidemia	287 (8.7)	16 (9.4)	33 (6.3)	141 (7.4)	0.137	0.106	110 (6.7)	121 (7.4)	0.453
Diabetes mellitus	962 (29.2)	54 (31.6)	141 (26.8)	531 (28.0)	0.475	0.349	436 (26.6)	445 (27.1)	0.723
Renal failure history	92 (2.8)	2 (1.2)	10 (1.9)	35 (1.8)	0.094	0.033	31 (1.9)	33 (2.0)	0.801
Heart failure history	103 (3.1)	5 (2.9)	15 (2.9)	29 (1.5)	0.006	<0.001	31 (1.9)	27 (1.6)	0.596
Hemorrhagic stroke	32 (1.0)	3 (1.8)	4 (0.8)	12 (0.6)	0.352	0.199	12 (0.9)	12 (0.7)	0.562
Ischemic stroke	418 (12.7)	21 (12.3)	75 (14.3)	210 (11.1)	0.171	0.084	184 (11.2)	186 (11.3)	0.912
Laboratory examinations									
Serum creatinine, mg/dL	1.10 (0.78–1.20)	1.03 (0.78–1.14)	1.03 (0.76–1.15)	1.04 (0.64–1.17)	0.180	0.063	1.05 (0.77–1.17)	1.05 (0.76–1.18)	0.933
Hemoglobin, g/dL	12.60 (11.50–13.90)	12.97 (11.70–14.40)	12.88 (11.80–14.10)	12.87 (11.70–14.10)	<0.001	<0.001	12.81 (11.70–14.00)	12.74 (11.60–14.00)	0.284
Clinical conditions									
GRACE score ≥140	2499 (75.9)	133 (77.8)	407 (77.4)	1443 (76.1)	0.846	0.884	1236 (75.3)	1282 (78.1)	0.058
Systolic blood pressure, mm Hg	131.75±23.57	128.64±24.83	133.12±24.24	130.76±25.23	0.077	0.157	130.22±23.11	129.76±25.37	0.591
Heart rate, beats per min	76.40±16.00	74.37±15.07	77.70±16.78	76.96±17.64	0.083	0.249	76.83±16.44	76.85±17.94	0.980
Killip class					<0.001	<0.001			0.001
Class I	1855 (56.3)	101 (59.1)	295 (56.1)	1254 (66.1)			1004 (61.1)	1024 (62.4)	
Class II to III	1237 (37.6)	58 (33.9)	205 (39.0)	499 (26.3)			546 (33.3)	477 (29.0)	
Class IV	201 (6.1)	12 (7.0)	26 (4.9)	144 (7.6)			92 (5.6)	141 (8.6)	
Type of ACS					<0.001	<0.001			0.350
STEMI	1681 (51.0)	120 (70.2)	318 (60.5)	1442 (76.0)			1172 (71.4)	1196 (72.8)	
NSTE-ACS	1612 (49.0)	51 (29.8)	208 (39.5)	455 (24.0)			470 (28.6)	446 (27.2)	

Continued

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Table 1. Continued

	Unmatched						Propensity Score–Matched		
	Nonloading (n=3293)	Only Aspirin Loading (n=171)	Only $P2Y_{12}$ Receptor Inhibitor Loading (n=526)	Dual Loading (n=1897)	*P* Value of 4 Groups*	*P* Value of Nonloading and Dual Loading Groups†	Nonloading (n=1642)	Dual Loading (n=1642)	*P* Value†
Hospital stays, d	11.58 (7.00–13.00)	10.26 (6.00–12.00)	11.31 (7.00–13.00)	11.82 (7.00–13.00)	0.879	0.749	11.11 (7.00–13.00)	12.17 (7.00–13.00)	0.232
Preadmission of oral antiplatelet therapy (within 2 wk until incidence of ACS)									
Aspirin	951 (28.9)	30 (17.5)	170 (32.3)	190 (10.0)	<0.001	<0.001	167 (10.2)	184 (11.2)	0.337
$P2Y_{12}$ receptor inhibitor	740 (22.5)	27 (15.8)	62 (11.8)	113 (6.0)	<0.001	<0.001	99 (6.0)	109 (6.6)	0.474
In-hospital medication									
Type of $P2Y_{12}$ receptor inhibitor used within 24 h of first medical contact					<0.001	<0.001			<0.001
Clopidogrel	3021 (91.7)	153 (89.5)	306 (58.2)	1371 (72.3)			1484 (90.4)	1207 (73.5)	
Ticagrelor	272 (8.3)	18 (10.5)	220 (41.8)	526 (27.7)			158 (9.6)	435 (26.5)	
ACEI or ARB	1703 (51.7)	80 (46.8)	245 (46.6)	866 (45.7)	<0.001	<0.001	845 (51.5)	744 (45.3)	<0.001
β-Blockers	1838 (57.7)	92 (55.4)	262 (52.0)	826 (46.0)	<0.001	<0.001	883 (55.4)	744 (45.3)	<0.001
Statins	3157 (96.0)	163 (95.3)	509 (97.0)	1814 (95.6)	0.562	0.529	1572 (95.8)	1569 (95.6)	0.734
Glycoprotein IIb/IIIa inhibitors	795 (24.1)	66 (38.6)	188 (35.7)	742 (39.1)	<0.001	<0.001	471 (28.7)	636 (38.7)	<0.001
Anticoagulant therapy					<0.001	<0.001			<0.001
None	925 (28.1)	35 (20.5)	107 (20.3)	1419 (24.1)			428 (26.1)	301 (18.3)	
UFH	57 (1.7)	1 (0.6)	8 (1.5)	100 (5.3)			39 (2.4)	91 (5.5)	
LMWH	2142 (65.0)	115 (65.5)	364 (69.2)	1364 (71.9)			1098 (66.9)	1186 (72.2)	
Fondaparinux	98 (3.0)	11 (6.4)	25 (4.8)	42 (2.2)			46 (2.8)	32 (1.9)	
Others	71 (2.2)	12 (7.0)	22 (4.2)	39 (2.1)			31 (1.9)	32 (1.9)	
Revascularization procedure									
Transradial access	3094 (94.0)	148 (86.5)	490 (93.2)	1731 (91.2)	<0.001	<0.001	1523 (92.8)	1502 (91.5)	0.174
Stents implantation	2623 (79.7)	148 (86.5)	409 (77.8)	1596 (84.1)	<0.001	<0.001	1372 (83.6)	1367 (83.3)	0.815
DES	2508 (76.2)	145 (84.8)	394 (74.9)	1586 (83.6)	<0.001	<0.001	1341 (81.7)	1355 (82.5)	0.524
In-admission CABG after PCI	24 (0.7)	2 (1.2)	1 (0.2)	11 (0.6)	0.405	0.528	9 (0.5)	10 (0.6)	0.819

Data are expressed as mean±SD, medians (25th–75th percentiles), or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; DES, drug-eluting stent; GRACE, Global Registry of Acute Coronary Events; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

*Chi-square tests were used for categorical variables. One-way ANOVA and Kruskal–Wallis tests were performed for continuous variables with normal and skewed distribution, respectively.

†Chi-square tests were used for categorical variables. *t* and Wilcoxon tests were used for continuous variables with normal and skewed distribution, respectively.

Table 2. In-Hospital Outcomes Within 15 d After Hospitalization*

	Unmatched						Propensity Score–Matched		
	Nonloading (n=3293)	Only Aspirin Loading (n=171)	Only $P2Y_{12}$ Receptor Inhibitor Loading (n=526)	Dual Loading (n=1897)	*P* Value of 4 Groups†	*P* Value of Nonloading and Dual Loading Groups†	Nonloading (n=1642)	Dual Loading (n=1642)	*P* Value†
MACE	57 (1.7)	1 (0.6)	9 (1.7)	57 (3.0)	0.009	0.003	34 (2.1)	49 (3.0)	0.153
Death	42 (1.3)	1 (0.6)	8 (1.5)	50 (2.6)	0.003	<0.001	27 (1.6)	44 (2.7)	0.044
Cardiac death	41 (1.2)	1 (0.6)	7 (1.3)	46 (2.4)	0.009	0.001	27 (1.6)	42 (2.6)	0.068
MI	6 (0.2)	1 (0.6)	0	7 (0.4)	0.205	0.195	0	0	
Stroke	15 (0.5)	1 (0.6)	4 (0.8)	21 (1.1)	0.049	0.006	8 (0.5)	18 (1.1)	0.049
Ischemic stroke	10 (0.3)	0	2 (0.4)	5 (0.3)	0.920	0.796	6 (0.4)	5 (0.3)	0.763
Stent thrombosis	5 (0.2)	0	0	4 (0.2)	0.831	0.623	1 (0.1)	3 (0.2)	0.317
All bleeding	157 (4.8)	9 (5.3)	30 (5.7)	203 (10.7)	<0.001	<0.001	88 (5.4)	181 (11.0)	<0.001
Major Bleeding	82 (2.5)	4 (2.3)	17 (3.2)	117 (6.2)	<0.001	<0.001	48 (2.9)	106 (6.5)	<0.001
Non–CABG-related major bleeding	81 (2.5)	4 (2.3)	17 (3.2)	116 (6.1)	<0.001	<0.001	47 (2.9)	105 (6.4)	<0.001

Data are expressed as number (percentage). CABG indicates coronary artery bypass grafting; MACE, major adverse cardiovascular event; MI, myocardial infarction.
*Patients may have had >1 outcome in each category but were counted only once for overall events.
†Chi-square tests were used for categorical variables. Fisher exact test was used as appropriate.

All *P* values were 2-tailed and a $P<0.05$ was considered statistically significant. All statistical analyses were conducted with SPSS 23.0 (IBM) and STATA 12.0 (StataCorp).

Results

Patients' Characteristics

A total of 5887 patients were enrolled in this study, with a mean age of 80.02 (SD 3.81) years and 37.4% women. The patients included 3293 in the nonloading group, 171 in the only aspirin loading group, 526 in the only $P2Y_{12}$ receptor inhibitors loading group, and 1897 in the dual loading group.

Characteristics of the study population were shown in Table 1. Among the 4 groups, there were fewer patients in the dual loading group with a history of MI (5.1%), PCI (6.0%), coronary artery bypass grafting (0.2%), heart failure (1.5%), and preadmission use of aspirin (10.0%) and $P2Y_{12}$ receptor inhibitors (6.0%). When comparing the clinical conditions at admission, patients in the dual loading group had a lower proportion of Killip class II to III (26.3%) but a higher proportion of class IV (7.6%). The dual loading group had more patients with ST-segment elevation MI (76.0%). Additionally, when comparing the treatment during hospitalization, patients in the dual loading group tended to use ticagrelor (27.7%), glycoprotein IIb/IIIa inhibitors (39.1%), and low-molecular-weight heparin (71.9%) and have stent implantation (84.1%). Patients in the nonloading group had the highest proportion of clopidogrel use (91.7%) and transradial access (94.0%) among the 4 groups. When we only compared the baseline characteristics between the nonloading group and the dual loading group, the above significant difference still existed. In addition, there were statistically significant differences in age (79.91±3.66 versus 80.20±4.02) and history of renal failure (2.8% versus 1.8%) between the nonloading and dual loading groups.

After propensity score matching, postmatching absolute standardized differences were <10% for all covariates (Figure S1). A total of 3284 cases, 1642 in each of the dual loading and nonloading groups, were matched. The characteristics of the dual loading and nonloading groups were recompared. In propensity score–matched population, there were no significant differences of baseline characteristics between the 2 groups except for Killip class and some in-hospital medications (Table 1).

Effectiveness Outcomes

In-hospital effectiveness outcomes within 15 days of admission were examined according to the different loading statuses. Among the whole study population, the incidence of in-hospital effectiveness outcome was much higher in the dual loading group (MACE: 3.0%; all-cause death: 2.6%) compared with the other groups (Table 2, Figure 2), mainly resulting from a high incidence of cardiac death. Cumulative hazards of MACE and all-cause death were also much higher in the dual loading group compared with other groups (Figure 3).

In the multivariate-adjusted analysis, a dual loading dose of aspirin and a $P2Y_{12}$ receptor inhibitor was associated with higher risk of in-hospital MACE (HR, 1.66; 95% CI, 1.13–2.44 [$P=0.010$]) (Table 3) and all-cause death (HR, 1.78; 95% CI,

Table 3. Independent Predictors of Primary Effectiveness Outcomes (MACE)

	HR (95% CI)	*P* Value
Whole study population		
DAPT loading statuses		
Only aspirin loading	0.34 (0.05–2.49)	0.291
Only $P2Y_{12}$ inhibitor loading	0.98 (0.48–2.00)	0.961
Dual loading	1.66 (1.13–2.44)	0.010
Age	1.09 (1.04–1.13)	<0.001
Female	1.45 (1.01–2.07)	0.043
Renal failure history	2.46 (1.21–5.03)	0.013
Heart rate	1.01 (1.01–1.02)	0.035
STEMI	1.80 (1.13–2.86)	0.013
Elevated serum creatinine level	2.08 (1.32–3.30)	0.002
Killip class		
Class II or III	2.13 (1.38–3.28)	0.001
Class IV	6.37 (3.94–10.29)	<0.001
Glycoprotein IIb/IIIa inhibitors	1.53 (1.05–2.22)	0.025
Transradial access	0.61 (0.38–1.00)	0.049
Stent implantation	0.48 (0.32–0.71)	<0.001
Propensity score–matched population		
Dual loading of antiplatelet therapy	1.36 (0.88–2.11)	0.168
Age	1.06 (1.01–1.11)	0.018
Female	1.67 (1.09–2.57)	0.020
Renal failure history	1.85 (0.70–4.87)	0.212
Heart rate	1.01 (1.00–1.02)	0.135
STEMI	1.41 (0.78–2.55)	0.253
Elevated serum creatinine level	2.77 (1.65–4.65)	<0.001
Killip class		
Class II or III	2.88 (1.68–4.95)	<0.001
Class IV	8.07 (4.43–14.69)	<0.001
Glycoprotein IIb/IIIa inhibitors	1.49 (0.95–2.35)	0.083
Transradial access	0.76 (0.41–1.41)	0.386
Stent implantation	0.42 (0.26–0.67)	<0.001

CI indicates confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACE, major adverse cardiovascular event; STEMI, ST-segment elevation myocardial infarction.

Table 4. Independent Predictors of Primary Safety Outcomes (Major Bleeding)

	HR (95% CI)	*P* Value
The whole study population		
DAPT loading statuses		
Only aspirin loading	0.86 (0.32–2.36)	0.775
Only $P2Y_{12}$ inhibitor loading	1.22 (0.72–2.06)	0.462
Dual loading	2.34 (1.75–3.13)	<0.001
Age	1.04 (1.00–1.07)	0.030
Female	1.10 (0.84–1.45)	0.486
Renal failure history	2.00 (1.09–3.67)	0.025
Elevated serum creatinine level	1.97 (1.36–2.86)	<0.001
Killip class		
Class II or III	1.39 (1.04–1.86)	0.028
Class IV	2.27 (1.52–3.38)	<0.001
Glycoprotein IIb/IIIa inhibitors	1.85 (1.41–2.42)	<0.001
Transradial access	0.48 (0.33–0.68)	<0.001
Propensity score–matched population		
Dual loading of antiplatelet therapy	2.08 (1.47–2.93)	<0.001
Age	1.06 (1.02–1.10)	0.002
Female	1.19 (0.86–1.64)	0.291
Renal failure history	2.64 (1.28–5.47)	0.009
Elevated serum creatinine level	1.51 (0.95–2.42)	0.082
Killip class		
Class II or III	1.64 (1.15–2.33)	0.006
Class IV	2.73 (1.73–4.32)	<0.001
Glycoprotein IIb/IIIa inhibitors	1.68 (1.26–2.33)	0.002
Transradial access	0.57 (0.37–0.89)	0.013

CI indicates confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio.

1.15–2.76 [*P*=0.010]) (Table S1) compared with dual nonloading of antiplatelet therapy.

After propensity score matching, the incidence of in-hospital MACE (3.0% versus 2.1%; *P*=0.153) and all-cause death (2.7% versus 1.6%; *P*=0.044) were still higher in the dual loading group but without statistical significance in MACE (Table 2, Figure 2). After multivariate-adjusted analyses, compared with the nonloading dose of antiplatelet agents, the dual loading dose of antiplatelet agents was associated with increased risk of MACE (HR, 1.36; 95% CI, 0.88–2.11 [*P*=0.168]) and all-cause death (HR, 1.57; 95% CI, 0.95–2.59 [*P*=0.079]), but without statistical significance (Table 3, Table S2).

Additionally, considering the impact of severe clinical conditions, we conducted further analysis by excluding patients with cardiac shock and cardiac arrest at admission, who were at the highest risk of death. We still did not observe a lower risk of in-hospital MACE in the dual loading group (whole population: HR, 1.85; 95% CI, 1.16–2.96 [*P*=0.010] and propensity score–matched population: HR, 1.80, 95% CI, 1.04–3.13 [*P*=0.035]).

Safety Outcomes

The incidence of major bleeding and all bleeding events within 15 days of admission was significantly higher in the dual

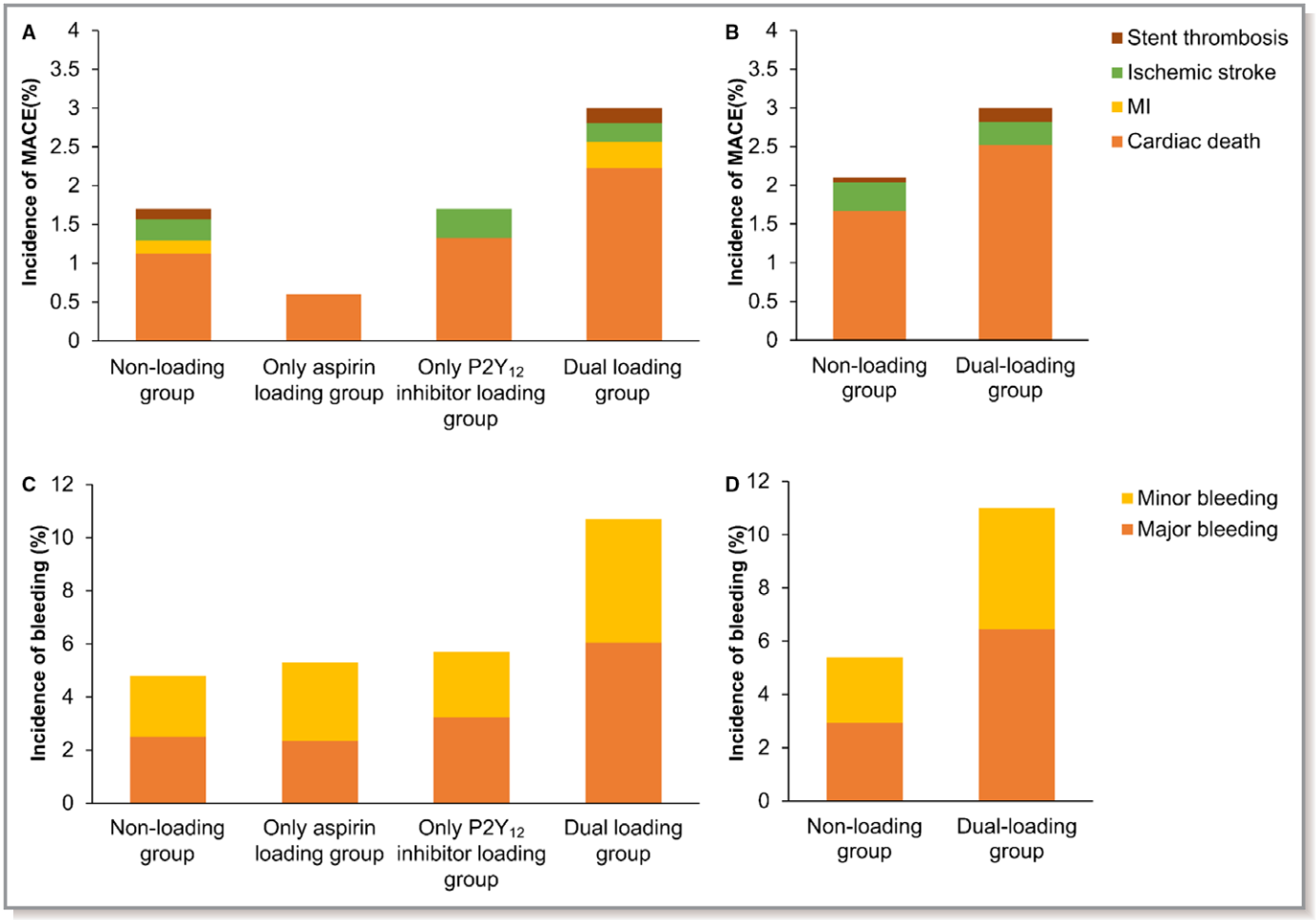

Figure 2. In-hospital outcomes within 15 days after hospitalization. The incidence of in-hospital primary effectiveness outcomes (major adverse cardiovascular event [MACE]) was higher in the dual loading group compared with other groups, mainly resulting from a higher proportion of cardiac death, in both the whole study population (A) and the propensity score–matched population (B). The incidence of both major bleeding and all bleeding was much higher in the dual loading group, compared with the nonloading group in both the whole study population (C) and the propensity score–matched population (D). The proportion of component outcomes is also shown by dosage categories. MI indicates myocardial infarction.

loading group than in the nonloading group in the whole study population (major bleeding: 6.2% versus 2.5%, $P<0.001$; all bleeding: 10.7% versus 4.8%, $P<0.001$) and the propensity score–matched population (major bleeding: 6.4% versus 2.9%, $P<0.001$; all bleeding: 11.0% versus 5.4%, $P<0.001$) (Table 2, Figure 2). The higher cumulative hazard of bleeding could be identified in the Kaplan–Meier curves (Figure 4).

In the multivariate analysis, the dual loading dose of aspirin and a $P2Y_{12}$ receptor inhibitor was associated with a 2-fold risk of in-hospital major bleeding (whole population: HR, 2.34; 95% CI, 1.75–3.13 [$P<0.001$] and propensity score–matched population: HR, 2.08; 95% CI, 1.47–2.93 [$P<0.001$]) (Table 4) and all bleeding events (whole population: HR, 1.98; 95% CI, 1.59–2.47 [$P<0.001$] and propensity score–matched population: HR, 1.97; 95% CI, 1.52–2.55 [$P<0.001$]) (Table S2).

Considering that patients in our study who received ticagrelor were more likely to take the loading dose, we used cross analyses between dosage and type of $P2Y_{12}$ inhibitor in the multivariate analysis in the propensity score–matched population to evaluate whether ticagrelor added to the risk of bleeding. However, compared with clopidogrel, ticagrelor was not associated with increased risk of major bleeding and all bleeding in this study. In addition, adding the type of $P2Y_{12}$ inhibitor did not change the association between loading dose and bleeding in the model (Tables S3 and S4).

Subgroup Analyses

Subgroup analyses were performed based on important baseline information in the whole study population and propensity score–matched population (Figures S2 through

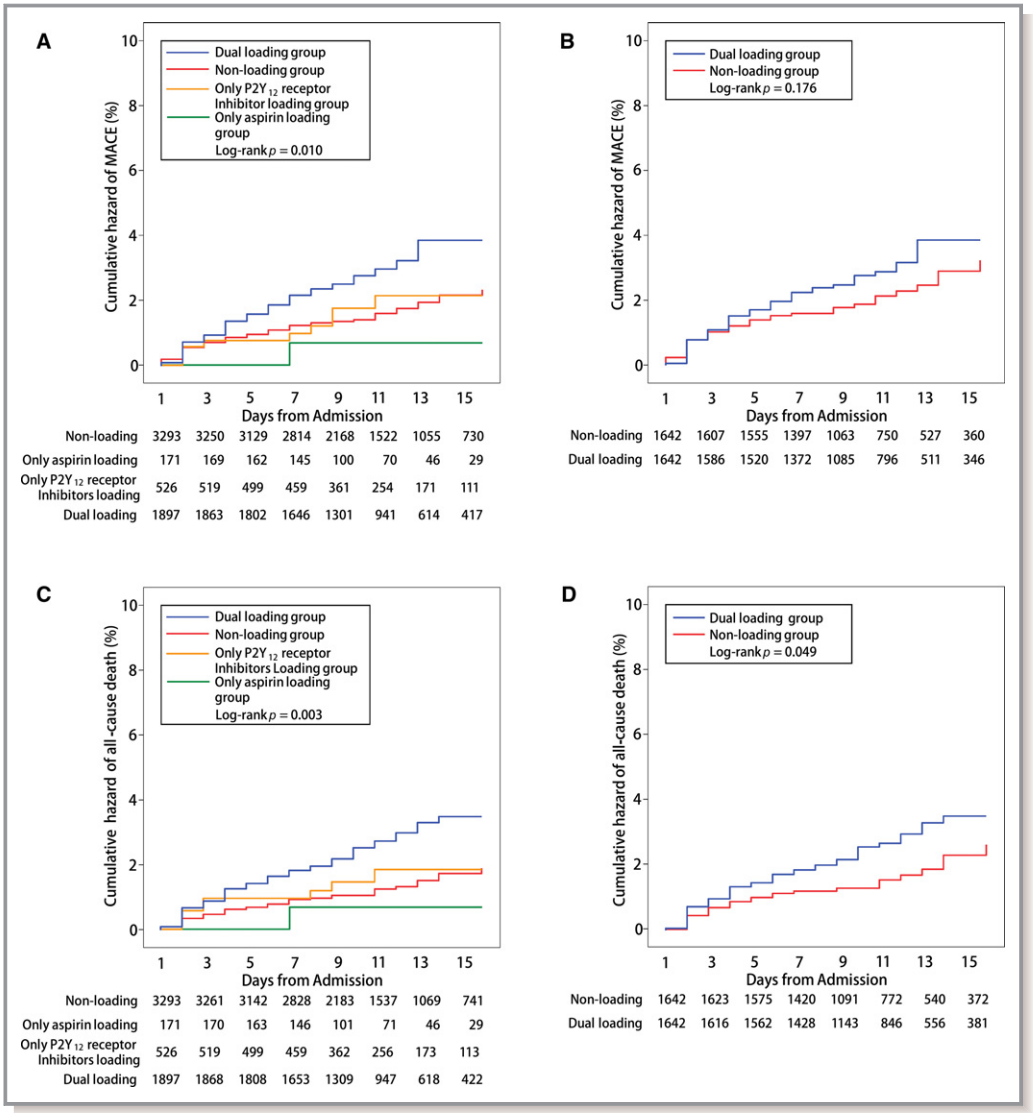

Figure 3. Cumulative Kaplan–Meier curve estimates of effectiveness outcomes during the 15-day in-hospital period. A and B, Data for the primary effectiveness outcomes of a major adverse cardiovascular event (MACE) in the whole study population and the propensity score–matched population, respectively. C and D, Data for the secondary effectiveness outcomes of all-cause death in the whole study population and the propensity score–matched population, respectively.

S5). Dual loading of aspirin and $P2Y_{12}$ receptor inhibitors was associated with an increased risk of MACE in most of the subgroups. No interactions were found in different subgroups in both the whole study population and the propensity score–matched population. Dual loading of antiplatelet therapy was also associated with increased risk of major bleeding in all subgroups. Hypertension and diabetes mellitus modified the association between a dual loading dose of antiplatelet therapy and major bleeding in the whole study population. A dual loading dose was associated with a 1.9-fold increased risk of major bleeding in patients without hypertension (HR, 1.87; 95% CI, 1.33–2.63) but a 3.8-fold risk in patients with hypertension (HR, 3.82; 95% CI, 2.05–7.13 [*P* value for interaction=0.026]). A dual loading dose was associated with a 1.4-fold risk of major bleeding in patients without diabetes mellitus (HR, 1.38; 95% CI, 0.80–2.37) and a 2.7-fold risk in patients with diabetes mellitus (HR, 2.68; 95% CI, 1.88–3.82 [*P* value for interaction=0.045]). The effect of hypertension was still observed in the propensity score–matched population (*P* value for interaction=0.011). No other interactions were found.

Discussion

Our study is the first registry study to examine the effect of dual loading versus nonloading doses of antiplatelet therapy

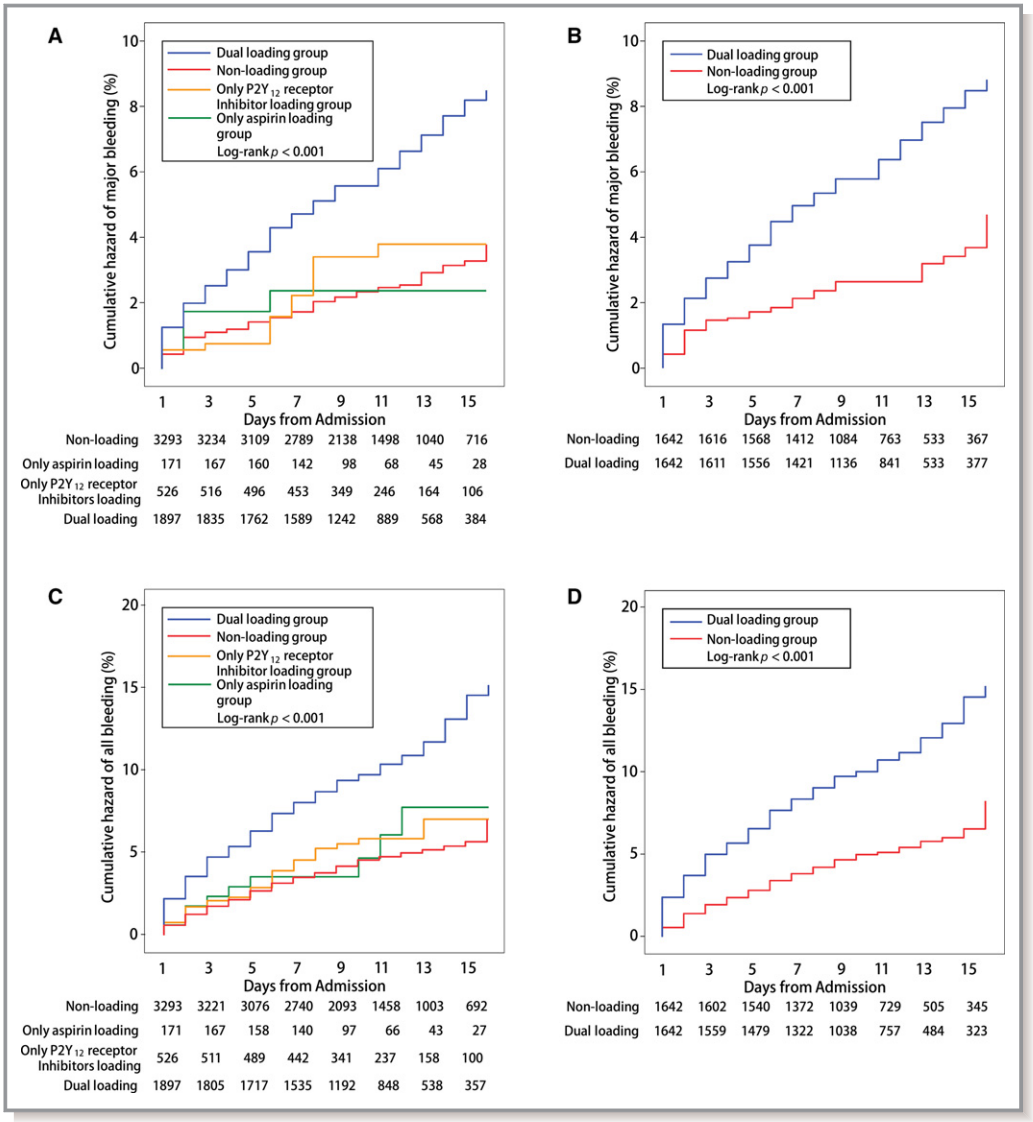

Figure 4. Cumulative Kaplan–Meier curve estimates of safety outcomes during the 15-day in-hospital period. A and B, Data for the primary safety outcomes of major bleeding in the whole study population and the propensity score–matched population, respectively. C and D, Data for the secondary safety outcomes of all-cause death in the whole study population and the propensity score–matched population, respectively.

on 15-day in-hospital outcomes of patients 75 years and older with ACS undergoing PCI. The present study showed that using dual loading antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor within 24 hours of first medical contact significantly increased the risk of major bleeding but was not associated with reduced risk of MACE.

Aging results in a series of physiological changes and comorbidities, which narrow the therapeutic ranges of several drugs and increase the risk of adverse drug-drug interactions.[8] This could potentially make older patients more prone to side effects and less to predictable effectiveness.[14] In current clinical practice, all patients with ACS undergoing PCI are recommended to receive standard therapy of antiplatelet agents, irrespective of age.[15] However, patients who are 75 years or older are often underrepresented or even excluded in randomized trials. Previous studies have determined that older patients have an independent risk of bleeding.[9] Independent of the underlying disorders, all antiplatelet drugs variously amplify age-related major risks of bleeding.[14] Therefore, when older patients receive a dual loading dose of antiplatelet therapy after having ACS, they might be at the highest risk of bleeding. In addition, few studies evaluated the effectiveness and safety of a dual loading dose of antiplatelet therapy.[1,16,17] Most of the recommendations in the guidelines for loading doses of aspirin and a $P2Y_{12}$ receptor inhibitor as early as possible or at the time of PCI were mostly based on observational data and experts' opinions, as no randomized controlled trials are available to inform this strategy.[2–5]

Recommendations on a loading dose of aspirin in ACS were originally from the period when only aspirin could be applied for oral antiplatelet therapy, and few studies evaluated the effect of loading dose, compared with nonloading dose in the acute phase.[17,18] The majority of studies on $P2Y_{12}$ receptor inhibitors evaluated the effectiveness of dual antiplatelet therapy (clopidogrel plus aspirin) versus aspirin alone or compared the effect of different kinds of $P2Y_{12}$ receptor inhibitors[19–21] or the effect of a high loading dose of $P2Y_{12}$ receptor inhibitors with a low loading dose of $P2Y_{12}$ receptor inhibitors.[16,22–24] Only 1 registry study compared the effect of a loading dose of clopidogrel with a standard dose in patients older than 75 years.[25] However, the use of aspirin was not mentioned in this study. The relatively small sample size of 791 patients in this study might not have been able to detect statistical significance in early complications. Therefore, whether older patients need to use a dual loading dose of antiplatelet therapy was based on relatively limited evidence.

Our study observed that a dual loading dose of antiplatelet therapy was associated with increased risk of major bleeding but not with decreased risk of MACE compared with dual nonloading antiplatelet therapy among patients 75 years or older with ACS undergoing PCI. These findings were consistent in the propensity score–matched population and subgroup analyses. The increased risk of major bleeding observed in the dual loading group is of concern. In our study, we found that the incidence of major bleeding was as high as 6.2% in the dual nonloading group, compared with 2.5% in the dual nonloading group. Bleeding is especially dangerous for older patients because it cannot only extend the length of hospital stay but may also result in death.[26] Additionally, bleeding can lead to the occurrence of ischemic events because antithrombotic therapy might be stopped when major bleeding occurs.[27] Therefore, further research is urgently required for studying the effectiveness and safety of antiplatelet therapy in patients 75 years and older.

Study Limitations

This was a real-word study. Therefore, the dose application of antiplatelet drugs in this study was not randomized but based on the doctor's judgment considering the patients' condition. However, after propensity score matching, we still observed a higher risk of bleeding in the dual loading group, but not with a lower risk of MACE. In addition, this study only analyzed in-hospital outcomes but without long-term evaluation. However, a previous study has shown that the different effects of initial antiplatelet agents occurred within 10 days according to different drug types or dosages.[28] Therefore, the effect of antiplatelet agents administrated within 24 hours of first medical contact would be expected to mainly be observed during hospitalization. Another limitation of our study is that we did not collect treatment information on proton pump inhibitors during hospitalization, which could lower the risk of bleeding, especially gastrointestinal bleeding. Further studies should take this issue into account. In addition, major bleeding was mainly defined based on the magnitude of decrease in hemoglobin, and the detailed information about bleeding site was unavailable in this study. Finally, all patients in this study were Chinese. Whether this result can be extrapolated to patients in non–East Asia needs further study.

Conclusions

Our study suggests that a dual loading dose of antiplatelet drugs within 24 hours of first medical contact were associated with increased risk of major bleeding but not with decreased risk of MACE among patients 75 years and older with ACS undergoing PCI. Therefore, clinicians should be cautious about administering a dual loading dose of antiplatelet therapy to patients 75 years and older with ACS undergoing PCI. However, more research is still needed to evaluate the effectiveness and safety of dual loading doses of antiplatelet therapy in this population.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Definition of acute coronary syndrome (ACS) and reperfusion strategies

ACS including ST-elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTE-ACS) was initially identified based on the principal discharge diagnosis obtained by reviewing the inpatient list for STEMI, non-ST elevation myocardial infarction and unstable angina. ACS was defined according to the guidelines for diagnosis and management of patients with STEMI (2010 and 2015) or NSTE-ACS (2012 and 2016) issued by the Chinese Society of Cardiology. These guidelines are based on chest pain, electrocardiography, and measurements of biomarkers of myocardial necrosis troponin I or troponin T, and are consistent with the definitions of STEMI and NSTE-ACS in the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines and the European Society of Cardiology (ESC) guidelines[1-4].

All patients included in this study have underwent early angiography and percutaneous coronary intervention (PCI). PCI was defined as percutaneous transluminal coronary angioplasty or stent(s) implantation at coronary lesion(s) that inducing ACS. Patients underwent rescued PCI after thrombolytic therapy were excluded.

Definition of other variables

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at admission, and having a history of hypertension or receiving antihypertensive therapy. Diabetes mellitus was defined as fasting blood glucose ≥7.0

mmol/L (126 mg/dL) or glycated hemoglobin A1c ≥ 6.5%, or having a history of diabetes mellitus, or receiving glucose-lowering drugs. Elevated serum creatinine level was defined as serum creatinine ≥ 1.5 mg/dL. Severe clinical conditions, including cardiac shock and cardiac arrest were defined as those with onset within 24 hours of current admission.

The Global Registry of Acute Coronary Events (GRACE) score was calculated based on the collected data. Other comorbidities were collected from medical record.

Doses of oral antiplatelet drugs

Among the whole study population (5887), there were 2068 patients taking loading dose (150mg to 325mg) of aspirin, of which 1997 (96.6%) took a dose of 300mg. On the other hand, there were 3819 patients taking non-loading dose of aspirin (50mg to 100mg) and 3796 (99.4%) of these 3819 patients took the dose of 100mg.

Similarly, among the whole study population (5887), there were 2423 patients taking loading dose of $P2Y_{12}$ inhibitors (746 and 1677 patients taking ticagrelor (180mg and 270mg) and clopidogrel (300mg to 600mg) respectively), of which 744 patients (99.7% of 746) took ticagrelor of 180mg and 1407 patients (84.0% of 1677) took clopidogrel of 300mg.

On the other hand, 3464 patients took non-loading dose of P2Y12 inhibitors (290 patients taking ticagrelor and 3174 taking clopidogrel). There were 283 patients (97.6% of 290) took ticagrelor of 90mg and 3004 patients (94.4% of 3174) took clopidogrel of 75mg.

Exclusion of patients as a result of lacking important clinical data

A total of 316 patients were excluded due to missing data of hemoglobin (214 patients), serum creatinine (136 patients), killip class (84 patients), heart rate (15 patients), blood pressure (14 patients), access site of PCI (85 patients), and past medical history (28 patients). Each of these patients may have more than one missing data but could be counted only once. These missing data were mainly due to the absence of records in patients' original medical records.

Table S1. Independent Predictors of Secondary Effectiveness Outcomes (All-cause death)

	HR (95% CI)	*p* value
Whole study population		
DAPT loading status		
Only aspirin loading	0.54 (0.07, 3.97)	0.547
Only $P2Y_{12}$ receptor inhibitor loading	1.09 (0.51, 2.37)	0.820
Dual loading	1.78 (1.15, 2.76)	0.010
Age	1.11 (1.04, 1.16)	<0.001
Female	1.52 (1.02, 2.27)	0.041
Renal failure history	2.84 (1.38, 5.84)	<0.001
STEMI	2.39 (1.33, 4.28)	<0.001
Elevated serum creatinine level	2.74 (1.72, 4.38)	<0.001
Killip class		
Class II, III	2.63 (1.58, 4.38)	<0.001
Class IV	6.77 (3.88, 11.83)	<0.001
Heart arrest	6.85 (3.66, 12.81)	<0.001
GPIIb/IIIa inhibitors	1.81 (1.20, 2.74)	0.005
Implantation of stent(s)	0.52 (0.33, 0.83)	0.006
Propensity score-matched population		
Dual loading of antiplatelet therapy	1.57 (0.95, 2.59)	0.079
Age	1.09 (1.04, 1.15)	0.001
Female	1.75 (1.09, 2.82)	0.021
Renal failure history	2.61 (1.06, 6.48)	0.038

STEMI	1.67 (0.80, 3.48)	0.176
Elevated serum creatinine level	3.78 (2.22, 6.44)	<0.001
Killip class		
Class II, III	4.11 (2.14, 7.91)	<0.001
Class IV	9.12 (4.45, 18.70)	<0.001
Heart arrest	6.35 (3.08, 13.13)	<0.001
GPIIb/IIIa inhibitors	1.95 (1.19, 3.20)	0.009
Implantation of stent(s)	0.44 (0.25, 0.77)	0.004

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; GP, glycoprotein; HR, hazard ratio; MACE, major adverse cardiovascular events; STEMI , ST-elevation myocardial infarction.

Table S2. Independent Predictors of Secondary Safety Outcomes (All bleeding)

	HR (95% CI)	*p* value
Whole study population		
DAPT loading status		
Only aspirin loading	0.85 (0.42, 1.74)	0.665
Only $P2Y_{12}$ receptor inhibitor loading	1.03 (0.69, 1.54)	0.882
Dual loading	1.98 (1.59, 2.47)	<0.001
Age	1.02 (1.00, 1.05)	0.070
Female	1.02 (0.83, 1.26)	0.834
Elevated serum creatinine level	1.69 (1.27, 2.25)	<0.001
Killip class		
Class II, III	1.38 (1.11, 1.71)	0.004
Class IV	1.60 (1.15, 2.23)	0.005
GPIIb/IIIa inhibitors	1.91 (1.55, 2.35)	<0.001
Transradial access	0.52 (0.39, 0.70)	<0.001
Propensity score-matched population		
Dual loading of antiplatelet therapy	1.97 (1.52, 2.55)	<0.001
Age	1.04 (1.01, 1.07)	0.008
Female	1.11 (0.87, 1.42)	0.411
Elevated serum creatinine level	1.46 (1.02, 2.10)	0.040
Killip class		0.004
Class II, III	1.40 (1.08, 1.82)	0.012
Class IV	1.72 (1.18, 2.52)	0.005

GPIIb/IIIa inhibitors	1.86 (1.45, 2.38)	<0.001
Transradial access	0.58 (0.41, 0.83)	0.002

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; GP, glycoprotein; HR, hazard ratio; MACE, major adverse cardiovascular events; STEMI, ST-elevation myocardial infarction.

Table S3. Independent Predictors of Major bleeding (Cross analyses between dosage and type of $P2Y_{12}$ inhibitors)

	HR (95% CI)	*p* value
Propensity score-matched population		
Loading status of antiplatelet therapy*		0.001
Non-loading doses of both ticagrelor and aspirin	1.43 (0.60-3.37)	0.420
Dual loading doses of both clopidogrel and aspirin	2.18 (1.49-3.18)	<0.001
Dual loading doses of both ticagrelor and aspirin	2.08 (1.27-3.39)	0.003
Age	1.06 (1.02-1.10)	0.001
Female	1.18 (0.86-1.63)	0.307
Renal failure history	2.61 (1.26-5.40)	0.010
Elevated serum creatinine level	1.53 (0.96-2.44)	0.076
Killip class		<0.001
Class II, III	1.64 (1.15-2.33)	0.006
Class IV	2.84 (1.81-4.48)	<0.001
GPIIb/IIIa inhibitors	1.74 (1.26-2.40)	0.001
Transradial access	0.55 (0.36-0.86)	0.009

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; GP, glycoprotein; HR, hazard ratio; MACE, major adverse cardiovascular events; STEMI, ST-elevation myocardial infarction.

*Non-loading dose of both clopidogrel and aspirin was reference standard.

Table S4. Independent Predictors of All Bleeding (Cross analyses between dosage and type of $P2Y_{12}$ inhibitors)

	HR (95% CI)	*p* value
Propensity score-matched population		
Loading status of antiplatelet therapy*		0.001
Non-loading doses of both ticagrelor and aspirin	1.39 (0.59-3.28)	0.455
Dual loading doses of both clopidogrel and aspirin	2.19 (1.50-3.19)	<0.001
Dual loading doses of both ticagrelor and aspirin	2.07 (1.27-3.38)	0.004
Age	1.06 (1.02-1.10)	0.001
Female	1.19 (0.86-1.64)	0.299
Renal failure history	2.62 (1.27-5.42)	0.009
Elevated serum creatinine level	1.51 (0.95-2.41)	0.083
Killip class		<0.001
Class II, III	1.66 (1.17-2.36)	0.005
Class IV	2.89 (1.84-4.56)	<0.001
GPIIb/IIIa inhibitors	1.76 (1.28-2.43)	0.001
Transradial access	0.56 (0.36-0.87)	0.009

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; GP, glycoprotein; HR, hazard ratio; MACE, major adverse cardiovascular events; STEMI, ST-elevation myocardial infarction.

*Non-loading dose of both clopidogrel and aspirin was reference standard.

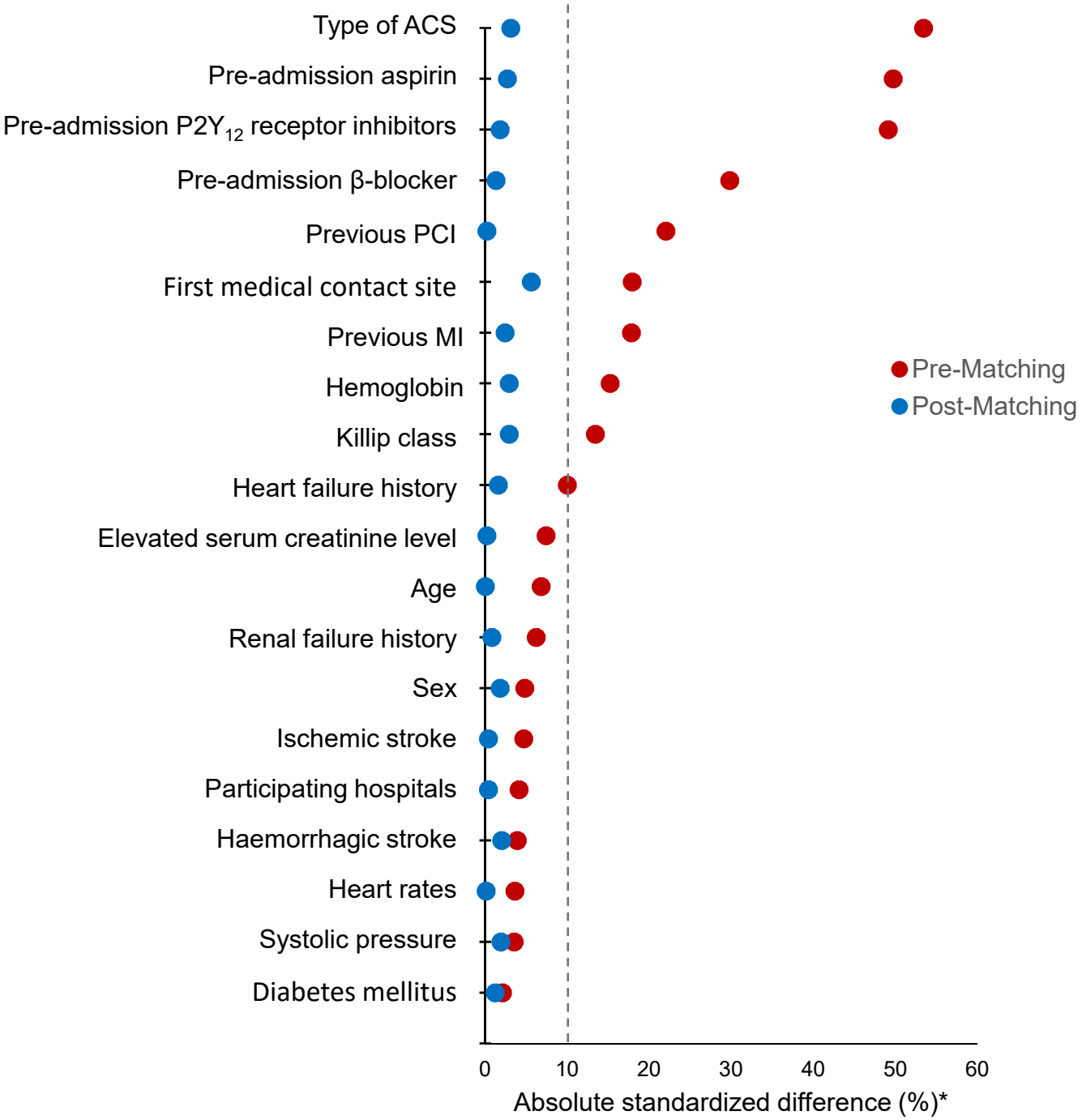

Figure S1. Absolute Standardized Differences Before and After Propensity Score Matching. ACS, acute coronary syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Post-matching standardized difference <10% indicates excellent covariate balance.

Subgroup	No. of patients	Non-loading n (%)	Dual loading n (%)	HR	95.0% CI	*p* for interaction
The whole population	5887	57 (1.7)	57 (3.0)	1.66	1.13-2.44	
Sex						0.144
Male	3684	28 (1.4)	32 (2.8)	2.19	1.28-3.73	
Female	2203	29 (2.4)	25 (3.4)	1.23	0.70-2.16	
Age						0.386
≥80	2565	27 (1.9)	31 (3.7)	1.99	1.15-3.44	
<80	3322	30 (1.6)	26 (2.5)	1.41	0.81-2.46	
Type of ACS						0.227
STEMI	3561	43 (2.6)	49 (3.4)	1.51	0.99-2.30	
NSTE-ACS	2326	14 (0.9)	8 (1.8)	2.80	1.13-6.95	
Pre-admission $P2Y_{12}$ receptor inhibitor						0.729
Yes	942	15 (2.0)	5 (4.4)	1.40	0.47-4.22	
No	4945	42 (1.6)	52 (2.9)	1.73	1.13-2.64	
Type of $P2Y_{12}$ receptor inhibitor used within 24 hours of first medical contact						0.284
Clopidogrel	4851	50 (1.7)	40 (2.9)	1.79	1.16-2.76	
Ticagrelor	1036	7 (2.6)	17 (3.2)	1.02	0.40-2.58	
Hypertension						0.919
Yes	4250	44 (1.8)	41 (3.0)	1.64	1.05-2.57	
No	1637	13 (1.5)	16 (2.9)	1.72	0.80-3.71	
Diabetes mellitus						0.867
Yes	1688	18 (1.9)	18 (3.4)	1.57	0.77-3.20	
No	4199	39 (1.7)	39 (2.9)	1.69	1.07-2.68	
GRACE score						0.400
≥140	4482	52 (2.1)	52 (3.6)	1.73	1.16-2.59	
<140	1405	5 (0.6)	5 (1.1)	0.95	0.25-3.61	
Killip class I						0.513
Yes	3505	16 (0.9)	19 (1.5)	1.24	0.62-2.49	
No	2382	41 (2.9)	38 (5.9)	1.94	1.22-3.09	
GPIIb/IIIa inhibitor						0.198
Yes	1791	25 (3.1)	27 (3.6)	1.29	1.27-2.28	
No	4096	32 (1.3)	30 (2.6)	2.14	0.73-3.61	

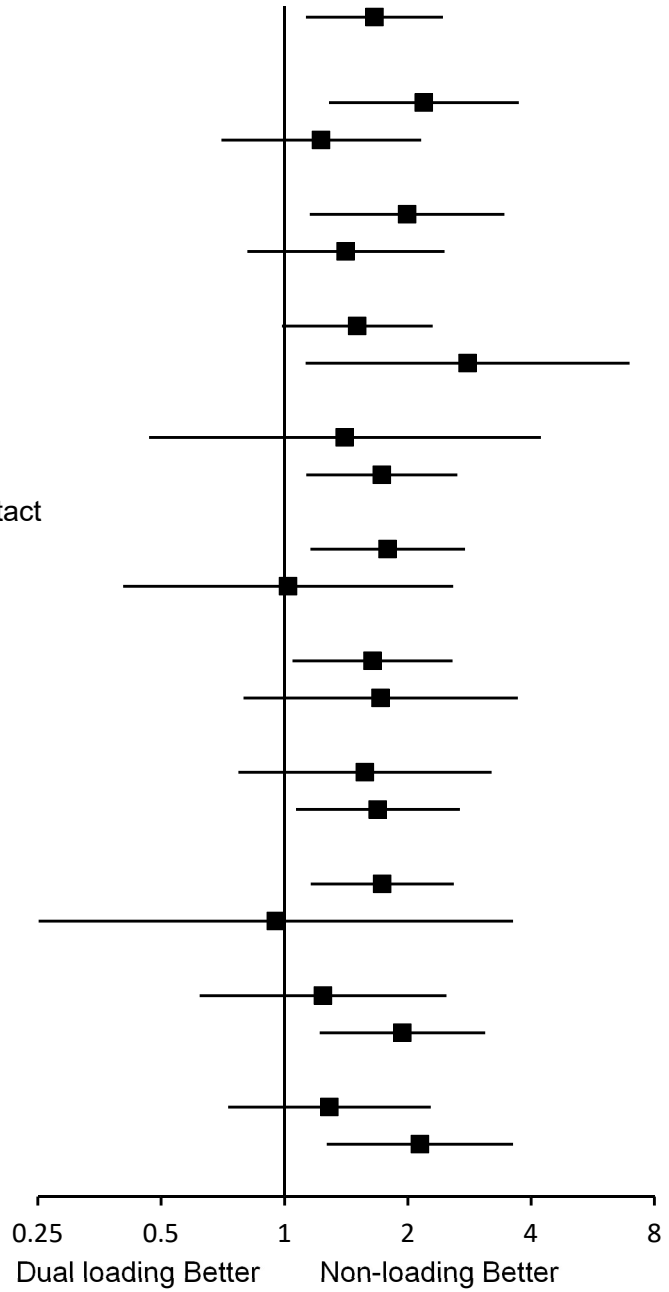

Figure S2. Subgroup Analyses for Primary Effectiveness Outcomes of the Whole Study Population. ACS, acute coronary syndrome; CI, confidence interval ; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio.

Subgroup	No. of patients	Non-loading n (%)	Dual loading n (%)	HR (95% CI)	HR	95.0% CI	*p* for interaction
The whole population	5887	82 (2.5)	117 (6.2)		2.34	1.75-3.13	
Sex							0.299
Male	3684	54 (2.6)	65 (5.6)		1.97	1.35-2.87	
Female	2203	28 (2.3)	52 (7.1)		2.72	1.68-4.39	
Age							0.407
≥80	2565	36 (2.5)	57 (6.8)		2.41	1.56-3.72	
<80	3322	46 (2.5)	60 (5.7)		2.13	1.42-3.20	
Type of ACS							0.443
STEMI	3561	56 (3.3)	97 (6.7)		2.04	1.46-2.86	
NSTE-ACS	2326	26 (1.6)	20 (4.4)		2.67	1.47-4.83	
Pre-admission $P2Y_{12}$ receptor inhibitor							0.245
Yes	942	22 (3.0)	5 (4.4)		1.29	0.47-3.56	
No	4945	60 (2.4)	112 (6.3)		2.43	1.76-3.36	
Type of $P2Y_{12}$ receptor inhibitor used within 24 hours of first medical contact							0.597
Clopidogrel	4851	74 (2.4)	85 (6.2)		2.32	1.68-3.21	
Ticagrelor	1036	8 (2.9)	32 (6.1)		1.84	0.82-4.11	
Hypertension							0.026
Yes	4250	67 (2.8)	78 (5.8)		1.87	1.33-2.63	
No	1637	15 (1.7)	39 (7.1)		3.82	2.05-7.13	
Diabetes mellitus							0.045
Yes	1688	30 (3.1)	28 (5.3)		1.38	0.80-2.37	
No	4199	52 (2.2)	89 (6.5)		2.68	1.88-3.82	
GRACE score							0.257
≥140	4482	73 (2.9)	94 (6.5)		2.08	1.51-2.85	
<140	1405	9 (1.1)	23 (5.1)		3.48	1.51-8.03	
Killip class I							0.335
Yes	3505	34 (1.8)	54 (4.3)		1.91	1.22-2.99	
No	2382	48 (3.3)	63 (9.8)		2.55	1.73-3.77	
GPIIb/IIIa inhibitor							0.758
Yes	1791	30 (3.8)	64 (8.6)		2.33	1.49-3.65	
No	4096	52 (2.1)	53 (4.6)		2.12	1.43-3.16	

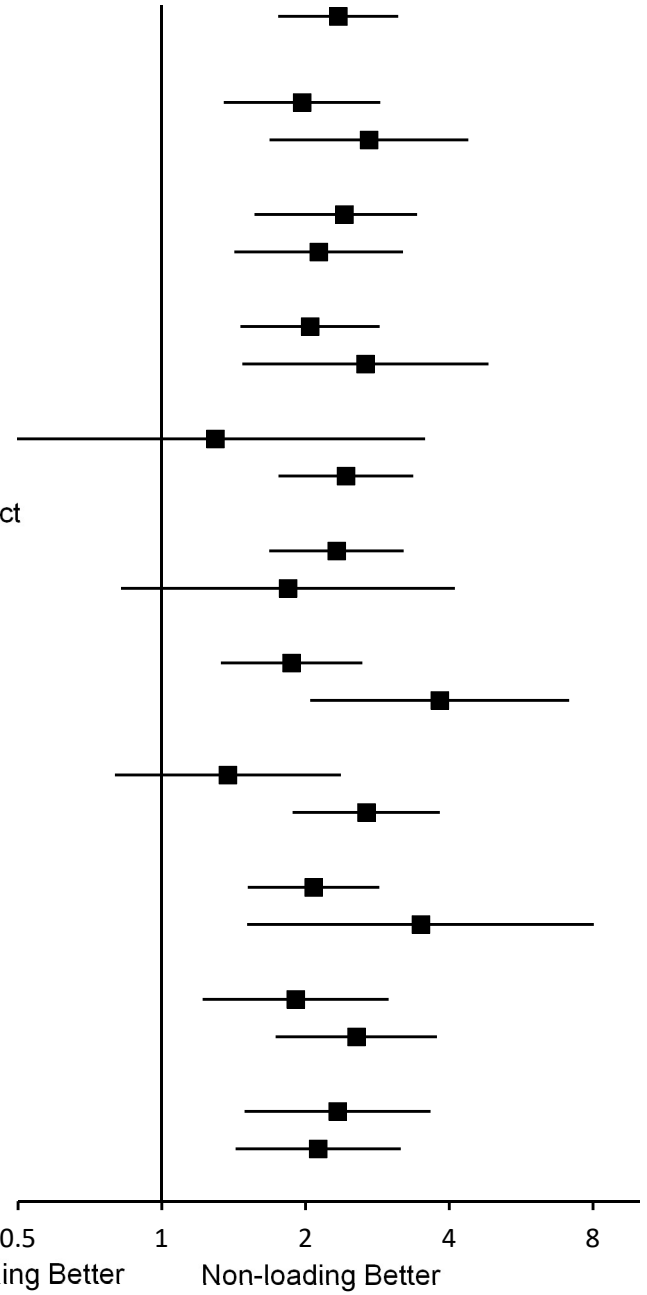

Figure S3. Subgroup Analyses for Primary Safety Outcomes of the Whole Study Population. ACS, acute coronary syndrome; CI, confidence interval ; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio.

Subgroup	No. of patients	Non-loading n (%)	Dual loading n (%)	HR (95% CI)	HR	95.0% CI	*p* for interaction
Propensity Score-Matched Population	3284	34 (2.1)	49 (3.0)		1.36	0.88-2.11	
Sex							0.165
Male	2034	15 (1.5)	27 (2.6)		1.93	1.01-3.66	
Female	1250	21 (3.3)	22 (3.6)		1.02	0.55-1.90	
Age							0.613
≥80	1440	18 (2.5)	24 (3.4)		1.52	0.81-2.85	
<80	1844	18 (2.0)	25 (2.7)		1.21	0.65-2.26	
Type of ACS							0.760
STEMI	2368	29 (2.5)	41 (3.4)		1.68	0.56-5.05	
NSTE-ACS	916	7 (1.5)	8 (1.8)		1.40	0.86-2.28	
Pre-admission $P2Y_{12}$ receptor inhibitor							0.380
Yes	208	4 (4.0)	5 (4.6)		0.63	0.11-3.51	
No	3076	32 (2.1)	44 (2.9)		1.4	0.88-2.22	
Type of $P2Y_{12}$ receptor inhibitor used within 24 hours of first medical contact							0.507
Clopidogrel	2691	31 (2.1)	34 (2.8)		1.41	0.86-2.32	
Ticagrelor	593	5 (3.2)	15 (3.4)		0.95	0.33-2.72	
Hypertension							0.829
Yes	2345	28 (2.4)	37 (3.2)		1.41	0.85-2.34	
No	939	8 (1.7)	12 (2.5)		1.25	0.50-3.15	
Diabetes mellitus							0.197
Yes	881	16 (3.7)	16 (3.6)		0.94	0.46-1.93	
No	2403	20 (1.7)	33 (2.8)		1.72	0.97-3.05	
GRACE score							0.967
≥140	2518	33 (2.7)	45 (3.5)		1.37	0.86-2.17	
<140	766	3 (0.7)	4 (1.1)		1.32	0.29-6.13	
Killip class I							0.812
Yes	2028	8 (0.8)	13 (1.3)		1.57	0.64-3.81	
No	1256	28 (4.4)	36 (5.8)		1.38	0.83-2.31	
GPIIb/IIIa inhibitor							0.532
Yes	1107	19 (4.0)	56 (8.8)		1.21	0.68-3.55	
No	2177	29 (2.5)	50 (5.0)		1.67	0.93-3.00	

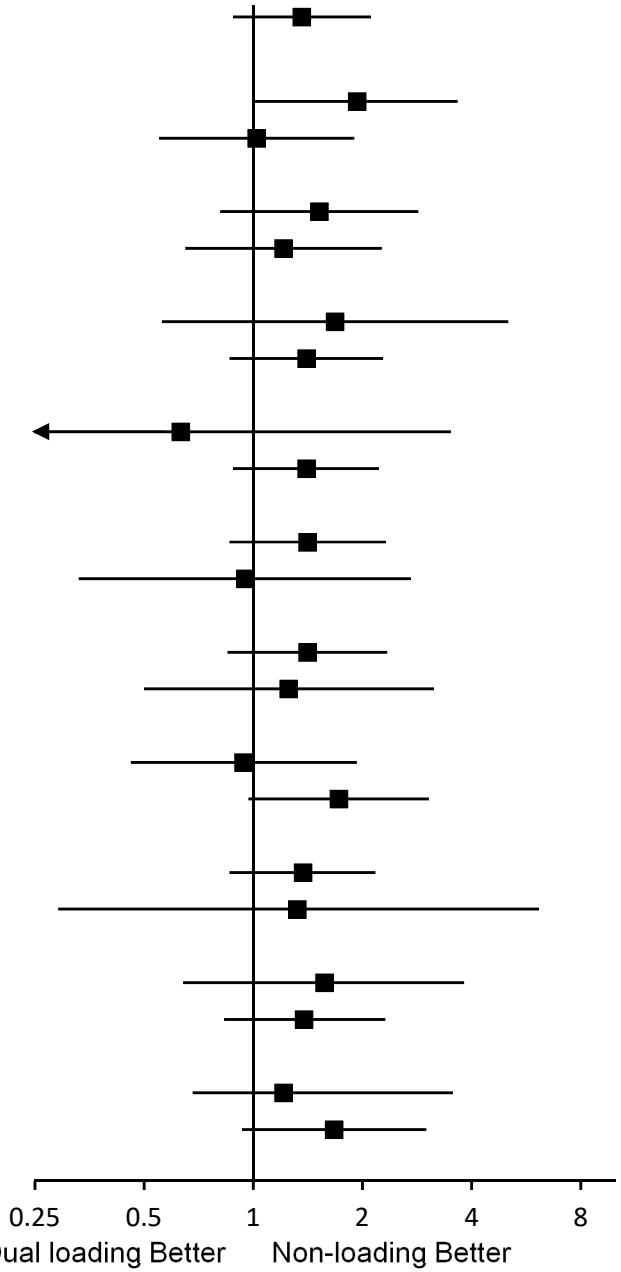

Figure S4. Subgroup Analyses for Primary Effectiveness Outcomes of the Propensity Score-Matched Population. ACS, acute coronary syndrome; CI, confidence interval ; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio.

Subgroup	No. of patients	Non-loading n (%)	Dual loading n (%)	HR (95% CI)	HR	95.0% CI	*p* for interaction
Propensity Score-Matched Population	3284	48 (2.9)	106 (6.5)		2.08	1.47-2.93	
Sex							0.706
Male	2034	29 (2.9)	61 (6.0)		1.95	1.25-3.05	
Female	1250	19 (3.0)	45 (7.3)		2.23	1.30-3.84	
Age							0.747
≥80	1440	26 (3.5)	51 (7.2)		1.96	1.22-3.15	
<80	1844	22 (2.4)	55 (5.9)		2.20	1.33-3.63	
Type of ACS							0.669
STEMI	2368	40 (3.4)	86 (7.2)		2.41	1.05-5.52	
NSTE-ACS	916	8 (1.7)	20 (4.5)		1.98	1.35-2.89	
Pre-admission $P2Y_{12}$ receptor inhibitor							0.584
Yes	208	1 (1.0)	5 (4.6)		3.88	0.42-36.11	
No	3076	47 (3.0)	101 (6.6)		2.07	1.46-2.93	
Type of $P2Y_{12}$ receptor inhibitor used within 24 hours of first medical contact							0.403
Clopidogrel	2691	42 (2.8)	79 (6.5)		2.22	1.52-3.25	
Ticagrelor	593	6 (3.8)	27 (6.2)		1.47	0.60-3.60	
Hypertension							0.011
Yes	2345	42 (3.5)	68 (5.9)		1.57	1.06-2.31	
No	939	6 (1.3)	38 (7.9)		5.37	2.25-12.82	
Diabetes mellitus							0.070
Yes	881	18 (4.1)	25 (5.6)		1.28	0.70-2.36	
No	2403	30 (2.5)	81 (6.8)		2.56	1.67-3.90	
GRACE score							0.425
≥140	2518	42 (3.4)	87 (6.8)		1.94	1.33-2.81	
<140	766	6 (1.5)	19 (5.3)		2.92	1.14-7.47	
Killip class I							0.435
Yes	2028	22 (2.2)	45 (4.4)		1.76	1.05-2.94	
No	1256	26 (4.1)	61 (9.9)		2.32	1.46-3.70	
GPIIb/IIIa inhibitor							0.783
Yes	1107	19 (4.0)	56 (8.8)		2.21	1.31-3.74	
No	2177	29 (2.5)	50 (5.0)		2.00	1.27-3.17	

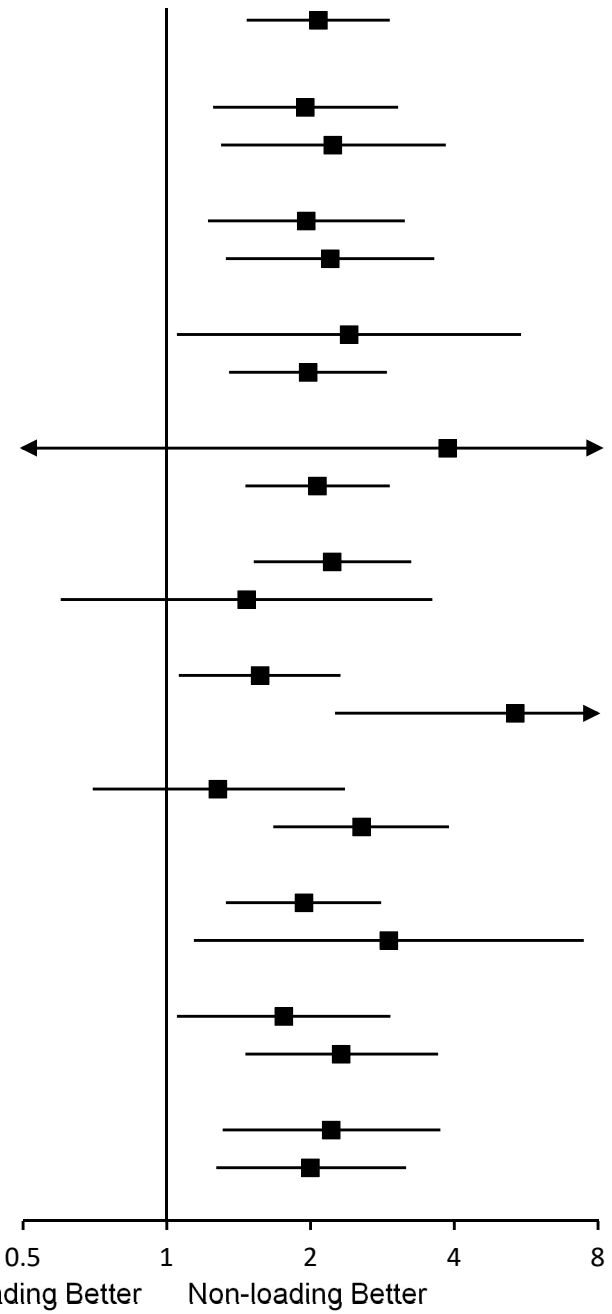

Figure S5. Subgroup Analyses for Primary Safety Outcomes of the Propensity Score-Matched Population. ACS, acute coronary syndrome; CI, confidence interval ; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio.

Supplemental References:

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2	Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School	Eastern China	Jiangsu	Nanjing	Biao Xu, Guangshu Han
3	Hainan General Hospital	Southern China	Hainan	Haikou	Bin Li
4	The Second Hospital of Jilin University	Northeast China	Jilin	Changchun	Bin Liu
5	The 2nd Affiliated Hospital of Harbin Medical University	Northeast China	Heilongjiang	Harbin	Bo Yu
6	The Ninth Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Eastern China	Shanghai	Shanghai	Changqian Wang
7	Henan Provincial People's Hospital	Central China	Henan	Zhengzhou	Chuanyu Gao
8	Shanxi Provincial People's Hospital	Northern China	Shanxi	Taiyuan	Chunlin Lai
9	Xinqiao Hospital, Third Military Medical University	Southwest China	Chongqing	Chongqing	Cui Bin, Lan Huang
10	China Meitan General Hospital	Northern China	Beijing	Beijing	Di Wu
11	The 309th Hospital of Chinese People's Liberation Army	Northern China	Beijing	Beijing	Fakuan Tang, Jun Xiao
12	Zhongda Hospital, Southeast University	Eastern China	Jiangsu	Nanjing	Genshan Ma
13	The First Affiliated Hospital of Liaoning Medical University	Northeast China	Liaoning	Jinzhou	Guizhou Tao
14	Xinjiang Uygur Autonomous Region People’s Hospital	Northwest China	Xinjiang	Urumchi	Guoqing Li
15	Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University	Eastern China	Zhejiang	Hangzhou	Guosheng Fu
16	Beijing Friendship Hospital, Capital Medical University	Northern China	Beijing	Beijing	Hongwei Li

17	The First Affiliated Hospital of Bengbu Medical College	Eastern China	Anhui	Bengbu	Honhju Wang
18	General Hospital of TISCO	Northern China	Shanxi	Taiyuan	Huifeng Wang
19	Dongguan People's Hospital	Southern China	Guangdong	Dongguan	Jianfeng Ye
20	Panyu Hospital of Chinese Medicine	Southern China	Guangdong	Guangzhou	Jianhao Li
21	Peking University First Hospital	Northern China	Beijing	Beijing	Jie Jiang
22	Sun Yat-sen Memorial Hospital, Sun Yat-sen University	Southern China	Guangdong	Guangzhou	Jingfeng Wang
23	Guangdong General Hospital	Southern China	Guangdong	Guangzhou	Jiyan Chen
24	Hospital of Xinjiang Production & Construction Corps	Northwest China	Xinjiang	Urumchi	Junming Liu
25	The Military General Hospital of Beijing PLA	Northern China	Beijing	Beijing	Junxia Li
26	The First Affiliated Hospital of Guangxi Medical University	Southern China	Guangxi	Nanning	Lang Li
27	Tongren Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Eastern China	Shanghai	Shanghai	Li Jiang
28	Binzou City Center Hospital	Eastern China	Shandong	Binzhou	Lijun Meng
29	The First Affiliated Hospital of Zhengzhou University	Central China	Henan	Zhengzhou	Ling Li
30	Xijing Hospital	Northwest China	Shaanxi	Xi'an	Ling Tao
31	The Affiliated Hospital of Guizhou Medical University	Southwest China	Guizhou	Guiyang	Lirong Wu
32	First Affiliated Hospital of the People's Liberation Army General Hospital	Northern China	Beijing	Beijing	Miao Tian
33	The Second People's Hospital of Yunnan Province	Southwest China	Yunnan	Kunming	Minghua Han
34	Haikou People's Hospital	Southern China	Hainan	Haikou	Moshui Chen
35	Gansu Provincial Hospital	Northwest China	Gansu	Lanzhou	Ping Xie

36	The First Affiliated Hospital of Henan University of Science and Technology	Central China	Henan	Luoyang	Pingshuan Dong
37	Chenzhou First People's Hospital	Central China	Hunan	Chenzhou	Qiaoqing Zhong
38	People’s Hospital of Qinghai Province	Northwest China	Qinghai	Xining	Rong Chang
39	Affiliated Hospital of Ningxia Medical University	Northwest China	Ningxia	Yinchuan	Shaobin Jia
40	Beijing Anzhen Hospital, Capital Medical University	Northern China	Beijing	Beijing	Shaoping Nie, Xiaohui Liu
41	North Jiangsu People's Hospital	Eastern China	Jiangsu	Yangzhou	Shenghu He
42	Shanghai Sixth People's Hospital	Eastern China	Shanghai	Shanghai	Shixin Ma
43	The First Hospital of Handan	Northern China	Hebei	Handan	Shuanli Xin
44	Huai'an First People's Hospital	Eastern China	Jiangsu	Huai'an	Shuren Ma
45	The First Affiliated Hospital of Chongqing Medical University	Southwest China	Chongqing	Chongqing	Suxin Luo
46	Navy General Hospital	Northern China	Beijing	Beijing	Tianchang Li
47	Zhejiang Provincial Hospital of TCM	Eastern China	Zhejiang	Hangzhou	Wei Mao
48	The Third Xiangya Hospital of Central South University	Central China	Hunan	Changsha	Weihong Jiang
49	Affiliated Hospital of Qinghai University	Northwest China	Qinghai	Xining	Weijun Liu
50	Teda International Cardiovascular Hospital	Northern China	Tianjin	Tianjin	Wenhua Lin
51	The Second Hospital of Hebei Medical University	Northern China	Hebei	Shijiazhuang	Xianghua Fu
52	Changhai Hospital of Shanghai	Eastern China	Shanghai	Shanghai	Xianxian Zhao
53	The Second Affiliated Hospital to Nanchang University	Eastern China	Jiangxi	Nanchang	Xiaoshu Cheng
54	Hebei General Hospital	Northern China	Hebei	Shijiazhuang	Xiaoyong Qi
55	Inner Mongolia People's Hospital	Northern China	Inner Mongolia	Hohhot	Xingsheng Zhao

56	The General Hospital of Shenyang Military Region	Northeast China	Liaoning	Shenyang	Yaling Han
57	The First Hospital of Jilin University	Northeast China	Jilin	Changchun	Yang Zheng
58	Tianjin Chest Hospital	Northern China	Tianjin	Tianjin	Yin Liu
59	Hunan Provincial People's Hospital	Central China	Hunan	Changsha	Ying Guo
60	People's Hospital of Yuxi City	Southwest China	Yunnan	Yuxi	Yinglu Hao
61	The People's Hospital of Guangxi Zhuang Autonomous Region	Southern China	Guangxi	Nanning	Yingzhong Lin
62	The First Teaching Hospital of Xinjiang Medical University	Northwest China	Xinjiang	Urumchi	Yitong Ma
63	Baogang Hospital	Northern China	Inner Mongolia	Baotou	Yongdong Li
64	Tianjin Medical University General Hospital	Northern China	Tianjin	Tianjin	Yuemin Sun
65	The Second Affiliated Hospital of Zhengzhou University	Central China	Henan	Zhengzhou	Yulan Zhao
66	Nanfang Hospital of Southern Medical University	Southern China	Guangdong	Guangzhou	Yuqing Hou
67	The First Affiliated Hospital to Nanchang University	Eastern China	Jiangxi	Nanchang	Zeqi Zheng
68	The First Affiliated Hospital of Lanzhou University	Northwest China	Gansu	Lanzhou	Zheng Zhang
69	The Third Hospital of Shijiazhuang	Northern China	Hebei	Shijiazhuang	Zhenguo Ji
70	Wuxi People's Hospital	Eastern China	Jiangsu	Wuxi	Zhenyu Yang
71	Jiangsu Province Hospital	Eastern China	Jiangsu	Nanjing	Zhijian Yang
72	The Second Hospital of Shanxi Medical University	Northern China	Shanxi	Taiyuan	Zhiming Yang
73	The Affiliated Hospital of Xuzhou Medical College	Eastern China	Jiangsu	Xuzhou	Zhirong Wang
74	Southwest Hospital, Third Military Medical University	Southwest China	Chongqing	Chongqing	Zhiyuan Song
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76	Yangzhou First People's Hospital	Eastern China	Jiangsu	Yangzhou	Aihua Li
77	Hospital 463 of Chinese People's Liberation Army	Northeast China	Liaoning	Shenyang	Bosong Yang
78	The Central Hospital of Mianyang	Northwest China	Sichuan	Mianyang	Caidong Luo
79	Liaocheng People's Hospital	Eastern China	Shandong	Liaocheng	Chunyan Zhang
80	Yancheng Third People's Hospital	Eastern China	Jiangsu	Yancheng	Chunyang Wu
81	The Second Xiangya Hospital of Central South University	Central China	Hunan	Changsha	Daoquan Peng
82	The Central Hospital of Panzhihua	Northwest China	Sichuan	Panzhihua	Dawen Xu
83	The First Hospital of Qiqihaer City	Northeast China	Heilongjiang	Qiqihaer	Gang Xu
84	The Third the People‘s Hospital of Bengbu	Eastern China	Anhui	Bengbu	Gengsheng Sang
85	The First Hospital of Jiamusi	Northeast China	Heilongjiang	Jiamusi	Guixia Zhang
86	Zhoushan People's Hospital	Eastern China	Zhejiang	Zhoushan	Guoxiong Chen
87	Dalian Municipal Central Hospital	Northeast China	Liaoning	Dalian	Hailong Lin
88	Renmin Hospital of Wuhan University	Central China	Hubei	Wuhan	Hong Jiang
89	Ningxia People's Hospital	Northwest China	Ningxia	Yinchuan	Hong Luan
90	The First People's Hospital of Yunnan Province (Kunhua Hospital)	Northwest China	Yunnan	Kunming	Hong Zhang
91	The Central Hospital of Zhoukou	Central China	Henan	Zhoukou	Hualing Liu
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93	Sichuan Provincial People’s Hospital	Northwest China	Sichuan	Chengdu	Jianhong Tao
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96	Qilu Hospital of Shandong University	Eastern China	Shandong	Jinan	Jifu Li

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102	Qingdao Municipal Hospital	Eastern China	Shandong	Qingdao	Jun Guan
103	Zhongshan Hospital Affiliated to Fudan University	Eastern China	Shanghai	Shanghai	Junbo Ge
104	Longyan First Hospital	Eastern China	Fujian	Longyan	Kaihong Chen
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107	Anhui Provincial Hospital	Eastern China	Anhui	Hefei	Likun Ma
108	Xiangtan City Central Hospital	Central China	Hunan	Xiangtan	Lilong Tang
109	The First Hospital of Haerbin City	Northeast China	Heilongjiang	Harbin	Lin Wei
110	Central Hospital Affiliated to Shenyang Medical College	Northeast China	Liaoning	Shenyang	Man Zhang, Kaiming Chen
111	The Central Hospital of Wuhan	Central China	Hubei	Wuhan	Manhua Chen
112	Hangzhou First People's Hospital	Eastern China	Zhejiang	Hangzhou	Ningfu Wang
113	The Central Hospital of Xuzhou	Eastern China	Jiangsu	Xuzhou	Peiying Zhang
114	The Second hospital of Dalian Medical University	Northeast China	Liaoning	Dalian	Peng Qu
115	The First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine	Northeast China	Liaoning	Shenyang	Ping Hou
116	Beijing Tsinghua Changgung Hospital	Northern China	Beijing	Beijing	Ping Zhang

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118	The First Affiliated Hospital of Xiamen University	Eastern China	Fujian	Xiamen	Qiang Xie
119	Quanzhou First Hospital	Eastern China	Fujian	Quanzhou	Rong Lin
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121	The Central Hospital of Jilin	Northeast China	Jilin	Changchun	Shuangbin Li
122	Xiangya Hospital Central South University	Central China	Hunan	Changsha	Tianlun Yang
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135	Tangdu Hospital of The Fourth Military Medical University	Northwest China	Shaanxi	Xi'an	Xue Li

136	Shanghai East Hospital Affiliated to Tongji University	Eastern China	Shanghai	Shanghai	Xuebo Liu
137	Xiamen Cardiovascular Disease Hospital	Eastern China	Fujian	Xiamen	Yan Wang
138	Zhongnan hospital of Wuhan University	Central China	Hubei	Wuhan	Yanggan Wang
139	Fujian Provincial Hospital	Eastern China	Fujian	Fuzhou	Yansong Guo
140	The First Affiliated hospital of Dalian Medical University	Northeast China	Liaoning	Dalian	Yanzong Yang
141	The First People's Hospital of Changde	Central China	Hunan	Changde	Yi Huang
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144	Cangzhou Central Hospital	Northern China	Hebei	Cangzhou	Zesheng Xu
145	The Central Hospital of Shaoyang	Central China	Hunan	Shaoyang	Zewei Ouyang
146	The People's Hospital of Liaoning Province	Northeast China	Liaoning	Shenyang	Zhanquan Li
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148	Tangshan Gongren Hospital	Northern China	Hebei	Tangshan	Zheng Ji
149	Huaibei Miners General Hospital	Eastern China	Anhui	Huaibei	Zhenqi Su
150	Linyi People's Hospital	Eastern China	Shandong	Linyi	Zhihong Ou