Contemporary invasive management and in-hospital outcomes of patients with non–ST-segment elevation myocardial infarction in China: Findings from China Acute Myocardial Infarction (CAMI) Registry

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Abstract Background Few studies have investigated the use of invasive strategy for patients with non–ST-segment elevation myocardial infarction (NSTEMI) in China. We aimed to describe the contemporary pattern of management, medically and invasively, in patients with NSTEMI across China.

Methods Using data of China Acute Myocardial Infarction Registry, we analyzed the baseline characteristics, in-hospital medication, index coronary angiography (CAG) and revascularization by stratification of gender, age, and risk assessment. Primary outcomes included in-hospital major adverse cardio-cerebral events (MACCE, a composite of all-cause death, myocardial (re)infarction, and stroke) and length of stay (LOS).

Results A total of 10,266 NSTEMI patients were enrolled between January 2013 and November 2016. Dual antiplatelet therapy and statins were prescribed in 92.9% and 92.1% of overall patients respectively. CAG was performed in 45.6% of these patients, and 40.9% had an index revascularization. Female, older or higher risk patients were less likely to receive CAG or revascularization. The rates of CAG were 67.9% in the provincial-level, 46.2% in the prefectural, and 12.1% in the county-level hospitals. Of those patients undergoing revascularization, 77.0% (1,156/1,501) very-high-risk patients received urgent revascularization and 16.2% (440/2,699) high-risk patients underwent early revascularization as recommended. The overall in-hospital MACCE was 6.7%, and the median LOS was 10 (6) days. Revascularization was associated with reduction for in-hospital MACCE regardless of risk and age.

Conclusion Invasive management was underused and profoundly deferred among patients with NSTEMI in China. The risk-treatment paradox, procedure deferral and medical resources distribution imbalance may represent opportunities for improvement. (Am Heart J 2019;215:1-11.)

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Hospitalization rate due to acute myocardial infarction (AMI) is constantly rising in China, and the increase in patients with non–ST-segment elevation myocardial infarction (NSTEMI) has become the major cause.[1-3] The mortality rate of patients with NSTEMI is equal to that of STEMI patients at the sixth month, and two times that in the fourth year.[4,5] Robust evidences have shown that early invasive strategy aiming for feasible revascularization is superior to conservative or selective strategy in NSTE-acute coronary syndrome (ACS) patients with reduction in all-cause mortality or myocardial infarction.[6-9] According to updated practice guidelines, urgent catheterization is indicated for NSTEMI patients stratified as very high-risk with ongoing signs and symptoms of ischemia as well as hemodynamic or electric instability. Otherwise, early revascularization should be considered for NSTEMI patients if initially stabilized.[8,9]

With the largest aging population in the world, the growing burden of NSTEMI in Chinese elderly is emerging.[10] In contrast to primary reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI), revascularization strategy based on risk stratification for NSTEMI patients were far from standardized in China. Recent data from tertiary hospitals showed that a substantial proportion of index PCI performed for NSTE-ACS in mainland China was deferred after 24 hours, suggesting that Chinese pattern of intervention for NSTEMI patients might be different from that of developed countries.[2] Furthermore, the underlying causes and its effect of the contemporary situation needs clarification to offer an opportunity for improvement. As the largest AMI registry study ever conducted in China, China AMI (CAMI) Registry offers representative Chinese study populations of acute MI in real world. Using data from CAMI Registry, we sought to investigate the baseline characteristics, in-hospital medication and invasive management and outcomes of patients with NSTEMI across Mainland China.

Methods

Study population

Consecutive NSTEMI cases enrolled in the CAMI registry between January 2013 and December 2016 were included in the study. The CAMI Registry is a prospective, nationwide, multicenter observational study for AMI patients in China. Its details have been described previously.[11] In brief, the registry includes 107 hospitals from all provinces and municipalities throughout Mainland China except Hong Kong and Macau. This project was approved by the institutional review board central committee at Fuwai Hospital, National Center for Cardiovascular Diseases of China and by the ethics committees of all participating institutions. Sites were instructed to enroll consecutive patients with a primary diagnosis of AMI. The study protocol was approved and written informed consent were obtained from all patients. This work was supported by CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-1-009), the Twelfth Five-Year Planning Project of the Scientific and Technological Department of China (2011BAI11B02), and 2014 Special fund for scientific research in the public interest by National Health and Family Planning Commission of the People's Republic of China (201402001). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

According to the third Universal Definition for Myocardial Infarction (2012), NSTEMI was defined as detection of a rise of cardiac troponin or creatine kinase-MB accompanied by either ischemic symptoms or electrocardiographic changes without new persistent ST-segment elevation.[12] Elevated cardiac enzymes were defined as a measurement exceeding the 99th percentile of the upper reference limit. Types 4a and type 5 are not eligible for the CAMI registry. We examined the baseline characteristics and in-hospital medication by stratification of gender and age (≤54 years, 55–64 years, 65–74 years, and ≥75 years). In-hospital treatment was also compared between patients of different GRACE risk profile, between hospitals of different level (provincial, prefectural, and county), and between patients with or without intra-hospital transfer. Timing of revascularization was examined based on the risk criteria mandating invasive strategy in NSTE-ACS recommended by European Society of Cardiology.[9] Patients were considered very high-risk when presented with hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure, or recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation. The other patients with NSTEMI were included in high-risk group for the rise of cardiac biomarkers, dynamic ST- or T-wave changes (symptomatic or silent), or Global Registry of Acute Coronary Events (GRACE) score ≫140.

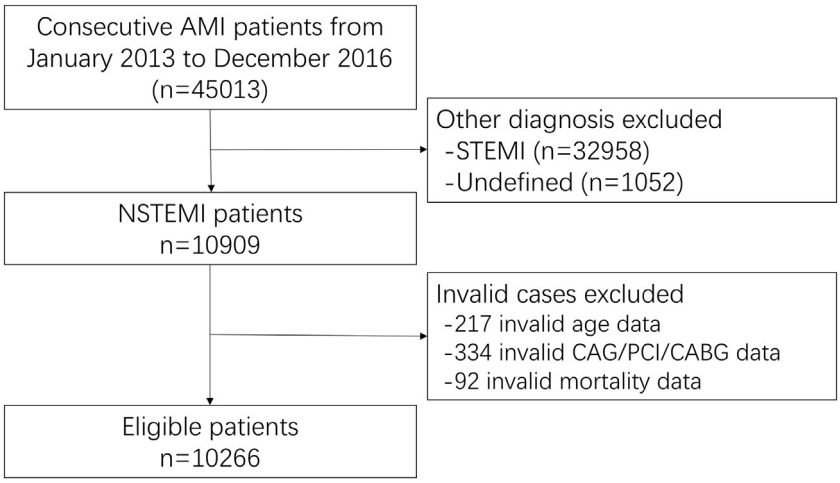
Data collecting

In CAMI Registry, all data were collected, validated, and submitted by the local investigators from participating sites through a secure, password-protected, web-based electronic data capture system (http://www.CAMIRegistry.org). Investigators were required to collect all the data during the hospitalization and submit the completed electronic case report form upon the patient's discharge or death. Data input tracking, regular alerts, rigorous data monitoring and queries are used to support timely and accurate completion of the electronic case report form.

Measurements

In the present study, we evaluated the application of revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) during the index hospitalization as well as guideline-recommended medical therapy, including aspirin, P2Y12 inhibitor, statins, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitor (ACEI) / angiotensin receptor blockers (ARBs), glycoprotein IIb/IIIa inhibitor (GPI), low-molecular-weight heparins (LMWH). For patients with urgent revascularization, the coronary angiography was required to be initiated within 2 hours after admission. For those with early revascularization, the coronary angiography should be performed within 72 hours after the event onset. The primary study endpoint was the in-hospital major adverse cardiac-cerebral events (MACCE). It's a composite of in-hospital all-cause death, myocardial (re)infarction, and stroke. Secondary endpoints included each component of the primary endpoint, major bleeding, new onset cardiac

Figure 1



Flow diagram of patient selection. AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction.

shock, and heart failure. LOS was defined as the difference in dates between discharge and admission.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using one-way ANOVA. Categorical variables were described using frequencies and percentages and compared using Chi-square test of Fisher's exact test, as appropriate. LOS was expressed as median (quartile) days. Trends across the age groups were evaluated by Mantel-Haenzsel Chi-square tests or Spearman's rank correlation test. All outcomes were compared between patients with revascularization and without according to risk and age stratification. Multivariable logistic regression models were introduced to assess the effect of revascularization on in-hospital mortality. The following variables were initially fitted in the model: age, sex, risk factors and comorbidities (current smoking, prior angina, prior MI, prior stroke, myocardial infarction, heart failure, previous PCI, previous CABG, diabetes, hypertension), GRACE risk score, and in-hospital treatment (aspirin, P2Y12 inhibitors, statins, β-blockers, calcium channel blockers, ACEI/ARBs, GPI, and heparins). Odds ratios (OR) were shown with 95% confidence intervals (CI) and corresponding *P*-values. All statistical analyses were performed using SAS software (version 9.4) and a 2-sided $P \ll .05$ was considered statistical significant.

Results

Baseline characteristics

During the study period, a total of 45,013 AMI patients were consecutively enrolled from 107 hospitals in CAMI registry. Among these hospitals, 31 were provincial-level (100% PCI capable), 45 prefectural-level (93% PCI capable), and 31 county-level (45% PCI capable). After excluding 32,958 (73.4%) patients with STEMI and 1052 (2.4%) undefined patients, a total number of 10,909 (24.3%) patients were diagnosed with NSTEMI. We excluded patients with invalid key values (n = 643). Finally, 10,266 NSTEMI patients were eligible for the analyses (Figure 1).

As shown in Table I, 3256 (31.7%) patients were female. 35.5% of overall patients (48.5% of male patients) were current smokers. Comorbidities of diabetes, hypertension and dyslipidemia accounted for 23.8%, 58.5%, and 8.1% of overall patients respectively. Female patients tended to be older and less likely current smoker (6.9% vs. 48.5%, $P \ll .001$) than male patients, and they more frequently had comorbidities of diabetes and hypertension. Older patients were more likely to be female and to have a history of myocardial infarction, heart failure and stroke. 38.1% of overall patients had a pre-hospital delay ≫24 hours after symptom onset. Female and older patients less frequently complain chest pain and tended to have a longer pre-hospital delay than their male or younger counterparts. On presentation, 5,555 patients (54.1%) were defined high risk according to GRACE score ≫140, and 3216 (31.3%) patients met at least one very-high-risk criterion based on the 2015 ESC guidelines for the management of NSTE-ACS patients. Proportion of high-risk patients was higher in female patients than male patients, and increased significantly with age.

In-hospital Medication

Aspirin and clopidogrel were given in 95.4% and 92.6% of all NSTEMI patients respectively, while ticagrelor was

Table I. Baseline clinical characteristics for patients with NSTEMI

	Overall n = 10266	Male n = 7010	Female n = 3256	≤54 years n = 2233	55–64 years n = 2676	65–74 years n = 2906	≥75 years n = 2451
Demographic							
Age (years)	67.74 ±13.33	62.60 ±13.50	69.36 ±11.68*	46.04 ±10.18	60.42 ±2.78†	69.91 ±2.88v	80.37 ±4.07†
Female, n (%)	3256 (31.7)	—	—	296 (13.3)	745 (27.8) †	1103 (38.0) †	1112 (45.4) †
BMI ≥ 28, n (%)	870 (8.5)	593 (8.5%)	277 (8.5%)	309 (13.8)	234 (8.7) †	200 (6.9) †	127 (5.2) †
Risk factor, n (%)							
Current smoker	3627 (35.3)	3401 (48.5)	226 (6.9)*	1292 (57.9)	1127 (42.1) †	777 (26.7) †	431 (17.6) †
Prior Angina	3404 (33.2)	2217 (31.6)	1187 (36.5)*	575 (25.8)	886 (33.1) †	1045 (36.0) †	898 (36.6) †
Prior MI	1166 (11.4)	849 (12.1)	317 (9.7)*	184 (8.2)	269 (10.1)	350 (12.0) †	363 (14.8) †
Prior stroke	1073 (10.5)	708 (10.1)	365 (11.2)	101 (4.5)	240 (9.0) †	383 (13.2) †	349 (14.2) †
Previous PCI	674 (6.6)	615 (7.4)	158 (4.9)*	142 (6.4)	174 (6.5)	204 (7.0)	154 (6.3)
Previous CABG	83 (0.8)	66 (0.9)	17 (0.5)	13 (0.6)	17 (0.6)	30 (1.0)	23 (0.9)
Chronic HF	571 (5.6)	328 (4.7)	243 (7.5)*	33 (1.5)	77 (2.9) †	196 (6.7) †	265 (10.8) †
Diabetes	2442 (23.8)	14445 (20.6)	998 (30.7)*	380 (17.0)	655 (24.5) †	795 (27.4) †	612 (25.0) †
Hypertension	6005 (58.5)	3794 (54.1)	2211 (67.9)*	1059 (47.4)	1497 (55.9) †	1836 (63.2) †	1613 (65.8) †
Hyperlipidemia	830 (8.1)	594 (8.5)	236 (7.2)	240 (10.7)	225 (8.4) †	219 (7.5) †	146 (6.0) †
On presentation							
No chest discomfort, n (%)	1079 (10.5)	603 (8.6)	476 (14.6)*	101 (4.5)	195 (7.3)	331 (11.4) †	452 (18.4) †
Pre-hospital delay »24h, n (%)	3103 (38.1)	2046 (36.7)	1057 (41.1)*	587 (33.3)	794 (37.3)	911 (39.6) †	811 (41.7) †
Malignant arrhythmia, n (%)	381 (3.7)	241 (3.4)	140 (4.3)	54 (2.4)	63 (2.4)	121 (4.2) †	143 (5.8) †
Heart rate (beat/min)	80.14 ±22.04	78.98 ±22.05	82.65 ±21.83*	77.96 ±25.56	78.09 ±19.56	80.40 ±20.38†	84.06 ±22.50†
Systolic blood pressure(mmHg)	134.19 ± 25.774	132.76 ± 24.89	137.26 ± 27.22*	131.435 ± 23.56	133.52 ±25.56	135.17 ± 25.83†	136.33 ± 27.41†
Killip class III–IV, n (%)	1186 (11.5)	703 (10.0)	483 (14.8)*	99 (4.4)	196 (7.3)	359 (12.4) †	532 (21.7) †
LV ejection fraction (%)	55.36 ±10.40	55.57 ±10.37	54.90 ±10.44	56.70 ±10.50	56.31 ±10.24	55.08 ±10.08†	53.41 ±10.53†
GRACE risk assessment							
Score	147.16 ±37.96	142.32± 37.80	157.59± 36.17*	112.10 ±26.84	135.82 ± 27.58†	156.42 ± 29.86†	180.50 ± 31.91†
High risk, n (%)	5555 (54.1)	3374 (48.1%)	2181 (67.0%)*	261 (11.7)	1070 (40.0) †	1997 (68.7) †	2227 (90.9) †
Risk criteria mandating invasive strategy in NSTE-ACS‡							
Very high, n (%)	3216 (31.3)	2062 (29.4)	1154 (35.4)*	543 (24.3)	712 (26.6) †	98 (34.3) †	963 (39.3) †

BMI: body mass index;
MI: myocardial infarction;
PCI: percutaneous coronary intervention;
CABG: coronary artery bypass graft;
HF: heart failure;
LV: left ventricle;
GRACE, Global Registry of Acute Coronary Events
* compared with male patients, $P \ll .001$
† compared with patients ≤54 years, $P \ll .001$;
‡ the risk criteria is based on the 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST- segment elevation.

rarely used (3.8%). The overall use rate of dual antiplatelet therapy was 92.9%. GPIs were given to 17.8% of overall patients. Female patients and those aged ≥75 years less frequently received aspirin, dual antiplatelet therapy and GPIs than their male or younger counterparts. Statins, β-blocker, ACEI/ARB, and LMWH were prescribed in 92.1%, 71.4%, 62.7%, and 86.2% of overall patients respectively. They were also less frequently used in patients aged ≥75 years when compared with other age groups. Female patients were less likely to receive β-blocker, GPIs, but more likely to receive calcium channel blockers than male patients (Table II). According to GRACE risk stratification, high-risk patients were less likely to receive all medications than those at low or moderate risk (Table III).

Invasive management

There were 4,684 (45.6%) patients underwent CAG and 4,200 (40.9%) patients received index revascularization in total. Among cases of revascularization, 97.5% were PCI and 2.5% were CABG. Female and older patients were less likely to undergo CAG or PCI than their male or younger counterparts (Table II). Patients of higher GRACE risk profile also less frequently received CAG or PCI (Table III). The provincial-level hospitals had the highest rates of CAG (67.9%) or PCI (58.9%) and the county-level hospitals had the lowest rates (12.1 for CAG and 10.0% for PCI). 2165 (21.1%) patients were transferred from one hospital to another, among which 61.1% underwent angiography and 55% received PCI. Lower-level hospitals were also less likely to perform an early revascularization than higher-level

Table II. In-hospital management and outcomes for patients with NSTEMI

	Overall n = 10266	Male n = 7010	Female n = 3256	≤54 years n = 2233	55–64 years n = 2676	65–74 years n = 2906	≥75 years n = 2451
Medication, n (%)							
Aspirin	9791 (95.4)	6713 (95.8)	3078 (94.5)*	2163 (96.9)	2596 (97.0)	2779 (95.6)†	2253 (91.9) †
Clopidogrel	9506 (92.6)	6507 (92.8)	2999 (92.1)	2060 (92.3)	2515 (94.0) †	2692 (92.6)	2239 (91.4) †
Ticagrelor	391 (3.8)	295 (4.2)	96 (2.9)	138 (6.2)	108 (4.0)	94 (3.2%)	51 (2.1) †
Dual antiplatelet therapy	9539 (92.9)	6574 (93.8)	2965 (91.1)*	2126 (95.2)	2549 (95.3)	2702 (93.0)	2162 (88.2) †
β-Blocker	7334 (71.4)	5083 (72.5)	2251 (69.1)*	1718 (76.9)	1991 (74.4)	2055 (70.7) †	1570 (64.1) †
ACEI/ARB	6441 (62.7)	4425 (63.1)	2016 (61.9)	1360 (60.9)	1669 (62.4)	1940 (66.8) †	1472 (60.1)
Calcium channel blockers	2134 (20.8)	1394 (19.9)	740 (22.7)*	454 (20.3)	555 (20.7)	593 (20.4)	532 (21.7)
Statin	9460 (92.1)	6439 (91.9)	3021 (92.8)	2088 (93.5)	2477 (92.6)	2678 (92.2)	2217 (90.5) †
Low molecular weight heparin	8849 (86.2)	6063 (86.5)	2786 (85.6)	1962 (87.9)	2346 (87.7)	2537 (87.3)	2004 (81.8) †
GP IIb/IIIa inhibitor	1828 (17.8)	1351 (19.3)	477 (14.6)*	505 (22.6)	567 (21.2)	491 (16.9) †	265 (10.8) †
Invasive management (%)							
Coronary angiography	4684 (45.6)	3532 (50.4)	1152 (35.4)*	1326 (59.4)	1477 (55.2) †	1259 (43.3) †	622 (25.4) †
PCI	4086 (39.8)	3093 (44.1)	993 (30.5)*	1180 (52.8)	1265 (47.3) †	1094 (37.6) †	547 (22.3) †
CABG	100 (1.0)	79 (1.1)	21 (0.6)	18 (0.8)	42 (1.6)	38 (1.3)	2 (0.1) †
Outcomes, n (%)							
Hospital stay [day, median (IQR)]	10 (6)	9 (7)	10 (7)*	9 (6)	9 (6)	10 (7) †	10 (8) †
New-onset heart failure	1642 (16.0)	943 (13.5)	699 (21.5)*	115 (6.8)	299 (11.2) †	520 (17.9) †	672 (27.4) †
Re-infarction	63 (0.6)	34 (0.5)	29 (0.9)	6 (0.3)	13 (0.5)	18 (0.6)	26 (1.1)
Stroke	72 (0.7)	35 (0.5)	37 (1.1)*	2 (0.1)	14 (0.5)	23 (0.8) †	33 (1.3) †
Major bleeding	71 (0.7)	40 (0.6)	31 (1.0)	5 (0.2)	11 (0.4)	23 (0.8)	32 (1.3) †
Death	602 (5.9)	326 (4.7)	276 (8.5)*	53 (2.4)	87 (3.3)	172 (5.9) †	178 (11.8) †
MACCE	690 (6.7)	374 (5.3)	316 (9.7)*	59 (2.6)	111 (4.1)	198 (6.8) †	322 (13.1) †

ACEI: angiotensin-converting enzyme inhibitor
ARB: angiotensin receptor blocker
PCI: percutaneous coronary intervention
CABG: coronary artery bypass graft
MACCE: major adverse cardiocerebrovascular events
* Compared with male patients, $P \ll .001$
† Compared with patients ≤54 years, $P \ll .001$.

Table III. In-hospital management based on GRACE risk stratification

	GRACE risk stratification		
	Low n = 1554	Moderate n = 3157	High n = 5227
Medication, n (%)			
Aspirin*	1520 (97.8)	3044 (96.4)	5227 (94.1)
Clopidogrel*	1460 (94.0)	2932 (92.9)	5114 (92.1)
Ticagrelor*	61 (3.9)	173 (5.5)	157 (2.8)
Dual antiplatelet therapy*	1489 (95.8)	2996 (94.9)	5054 (91.0)
β-blocker*	1210 (77.9)	2413 (76.4)	3711 (66.8)
ACEI/ARB*	1037 (66.7)	2072 (65.6)	3332 (60.0)
Calcium Channel Blockers*	379 (24.4)	712 (22.6)	1043 (18.8)
Statin*	1444 (92.9)	2941 (93.2)	5075 (91.4)
Low molecular weight heparin*	1381 (88.9)	2785 (88.2)	4683 (84.3)
GP IIb/IIIa inhibitor*	330 (21.2)	645 (20.4)	853 (15.4)
Invasive management (%)			
Coronary angiography *	936 (60.2)	1773 (56.2)	1975 (35.6)
PCI*	845 (54.4)	1551 (49.1)	1690 (30.4)
CABG	12 (0.8)	42 (1.3)	46 (0.8)

ACEI: angiotensin-converting enzyme inhibitor;
ARB: angiotensin receptor blocker;
PCI: percutaneous coronary intervention;
CABG: coronary artery bypass graft;
MACCE: major adverse cardiocerebrovascular events.
* $P \ll .001$.

hospitals. No difference could be found in timing of revascularization between patients with and without transfer (Table IV). According to updated guidelines, 3,216 (31.3%) patients were stratified as very high-risk, and 7,050 (68.7%) as high-risk. Of those very-high-risk patients who underwent index revascularization, 77% (n = 1,156) received urgent revascularization as guideline recommended. Of those high-risk patients undergoing revascularization, only 16.2% (n = 440) had early revascularization while 45.1% (n = 1,216) had the procedure after 7 days. The rate of revascularization decreased significantly with age in both risk groups. Older patients were more likely to defer revascularization than their younger counterparts (Figure 2).

In-hospital outcomes

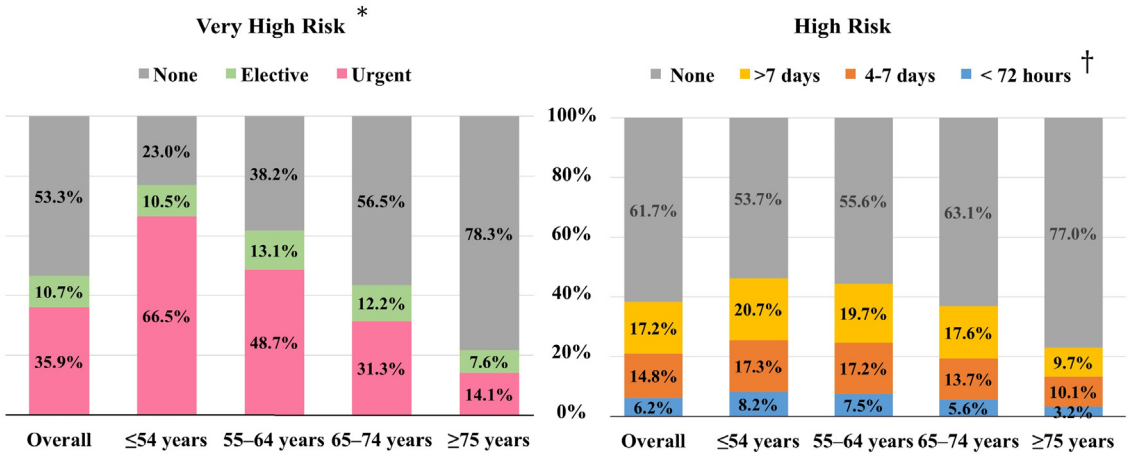
The rate of in-hospital MACCE in overall patients were 6.7%. Female and older patients had a higher rate of MACCE, death, stroke, and new-onset heart failure than their male or younger counterparts (Table II). Very-high-risk patients had a significantly higher MACCE than high-risk patients (11.3% vs. 4.7%, $P \ll .001$). MACCE was less frequently observed in patients undergoing revascularization than in those without revascularization in both risk groups (very high-risk patients: 2.9% vs. 18.6%, $P \ll .001$; high-risk patients: 1.4% vs. 6.7%, $P \ll .001$). Regardless of

Table IV. Invasive management in hospitals of different level and patients with or without transfer

	Level of hospital			Intra-hospital transfer	
	provincial n = 2492	prefectural n = 6395	County n = 1379	Transferred n = 2165	No transfer n = 8101
Coronary angiography	1693 (67.9)	2956 (46.2)*	167 (12.1)*	1322 (61.1)	3362 (41.5) †
Revascularization					
PCI	1190 (58.9)	2896 (38.8)*	138 (10.0)*	1190 (55.0)	2896 (35.7) †
CABG	54 (2.2)	39 (0.6)*	7 (0.5)*	24 (1.1)	76 (0.9)
Timing of revascularization‡					
≪72h	594 (38.7)	712 (28.3)*	33 (22.8)*	367 (30.1)	972 (32.6)
»7d	462 (30.1)	1047 (41.5)*	51 (35.2)*	472 (38.8)	1088 (36.5)

PCI: percutaneous coronary intervention;
CABG: coronary artery bypass graft;
MACCE: major adverse cardiocerebrovascular events.
* compared with provincial hospitals, $P \ll .001$;
† compared with transferred patients, $P \ll .001$;
‡ time from symptom onset.

Figure 2



Use and timing of revascularization in patients with NSTEMI based on risk stratification. *Very high risk criteria mandating invasive strategy in NSTE-ACS included hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure, or recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation. †Time from revascularization to symptom onset.

risk profile or age, patients undergoing revascularization were less likely to develop cardiogenic shock, new onset heart failure, or recurrent ischemia during their hospital stay. Patients with revascularization had fewer major bleeding complications. (Table V). Multivariate logistic regression analysis showed that revascularization was associated with significant reduction of in-hospital MACCE in overall patients (OR 0.33, 95% CI 0.25-0.42, $P \ll .001$), regardless of risk profile or age (Figure 3).

The overall median (IQR) LOS was 10 (6) days. Female and older patients had a longer LOS than the male or younger counterparts (Table II). In total, patients with an index revascularization had a longer LOS, regardless of age (Table V).

Discussion

Based on the largest Chinese national registry platform of AMI, the present study delineated the current revascularization pattern of NSTEMI patients across mainland China. Although the use of guideline-recommended medication were less used in female and older patients, the overall antiplatelet and other medical therapy was approaching to the situation of developed countries. However, index CAG or revascularization remained underused in NSTEMI patients in China, especially in the female and older patients. The most striking finding was that a large proportion of revascularization performed in NSTEMI patients was deferred for over 3 days after event onset, especially in those who

were initially stabilized. Although revascularization was shown to be associated with benefit against in-hospital MACCE in all patients, it may also be associated with prolonged LOS.

In the United States, the proportion of NSTEMI had already exceeded that of STEMI after 2000 due to the widespread adoption of troponin for diagnosing AMI, the aging of the population, and the greater use of guideline-recommended medical therapy.[13] China is currently experiencing many of the same demographic and medical changes as the United States did in 1990s. However, the present study showed that NSTEMI patients made up only a quarter of overall AMI patients in China, and there seemed to be no change of the in-hospital dominance of STEMI throughout the last two decades.[1,14] Murugiah et al demonstrated that biomarker use and hospital characteristics did not account for the low NSTEMI rate in China.[10] From our perspective, there are several conceivable explanations for the persistent dominance of STEMI. First, STEMI-related risk factors, like smoking, unhealthy diet and lifestyles, and hypertension etc., are not yet well controlled in Mainland China Nowadays, and the work pressure and anxiety are dramatically increasing due to fast economy growing. Such risk factors tend to cause more STEMI than NSTEMI. Second, the manifestation of NSTEMI often appear not so critical as that of STEMI, so that the patients or their relatives are unaware of the severity of their situation and fail to get medical service help in time. Third, NSTEMI patients tend to be older. Chinese traditional culture makes them feel guilty to bother their younger offspring and they tend to refuse treatment for the concern of medical expenses. More specific questionnaire may be need to verify the underlying causes.

There seemed to be interesting differences in risk factors between China and other countries (Table VI). Diabetes prevalence in our NSTEMI cohort was lower than that of the United States and other Asian countries like 33.8% in Korea Acute Myocardial Infarction Registry (KAMIR).[15] In fact, the general prevalence of diabetes in China, although sharply increased (from 1% in 1980 to 10.9% in 2013), was still lower than those in Asian developed countries like Japan (12.1%), South Korean (13.7%), and Singapore (about 20%) at the same period.[16] Awareness rate of diabetes remained relatively low in China, especially in less-developed districts. Additionally, we only included the patients' past history, so newly diagnosed diabetes were not included. Chinese patients tended to have a higher rate of smoking than west countries due to the extremely high smoking rate of male patents.

It was not until recently that the Improving CCC (Care for Cardiovascular Disease in China) Project described the antithrombotic and invasive management for patients with NSTE-ACS (74.3% were NSTEMI) in China.[2] In line with the findings of Improving CCC Project, our data from CAMI Registry showed that a large proportion of NSTEMI patients had received early dual antiplatelet treatment and other guideline-recommended drugs, such as statins, LMWH, β-blokers, and ACEI/ARBs. This was similar to that documented by other registries.[17-20] The highly compliance to updated guidelines, even in elderly patients, was directly due to increased efforts Chinese doctors had made to promote evidence-based treatment.

However, the efforts seemed to be "missing" in terms of invasive management for those patients. A considerable discrepancy was discovered between guideline recommendations and the actual practice pattern of CAG or revascularization for NSTEMI patients in China. Only 40.9% of patients had received index revascularization, which was much lower than that of United States (58.1%) and South Korea (79.1%).[21] It was even lower than the revascularization rate reported by Improving CCC Project (58.2%) in Chinese NSTE-ACS patients.[2] Based on the robust evidence favoring invasive strategy over conservative treatment, the lower rate of utilization of CAG or revascularization might contribute at least partly to the higher in-hospital mortality of NSTEMI patients in China (6.1%) compared with developed countries like the United States (3.9%),[22] Australia and New Zealand (4.0%),[23] Sweden (5.2%),[24] and South Korea (4.5%).[21]

There were several possible factors which might limit the utilization of invasive management in China. First, the higher risk NSTEMI patients received less in-hospital invasive management. Such a risk-treatment paradox had been well established in other registry studies,[25] and the cause has not been sufficiently studied. It could partly be explained by clinicians' reluctance to perform invasive procedures in patients perceived to be at high risk for developing procedure related complications, like female and older patients. In line with other studies concerning impact of aging,[19,26-28] the present study showed that regardless of risk profiles, advanced age was a major factor limiting the utilization of revascularization for NSTEMI patients in China. After randomized trials like the Italian Elderly ACS study[7] and the After Eighty trial,[29] it is widely accepted that coronary angiography followed by revascularization is safe and beneficial by reducing mortality and myocardial (re)infarction rate in elderly patients aged ≥75 years with NSTE-ACS. The significant reduction of in-hospital mortality associated with revascularization across all age groups in our study also highlighted that advanced age per se should not be considered a contraindication to revascularization following presentation with NSTEMI. Since the number of Chinese elderly is increasing dramatically due to aging of population, the need to distinguish more elderly patients with NSTEMI as candidates for a feasible early revascularization is still relatively unmet. Second, unlike the Improving CCC project which only involved tertiary hospitals, CAMI took into account the practice pattern of hospital of different levels. The lack of PCI facilities and

Table V. In-hospital outcomes of patients with NSTEMI according to revascularization

	Overall (n = 10266)		Risk stratification			
			Very high risk (n = 3216)		High risk (n = 7050)	
	+ (n = 4200)	- (n = 6066)	+ (n = 1501)	- (n = 1715)	+ (n = 2699)	- (n = 4351)
LOS [day, median (IQR)]	10 (7,13)	9 (6, 13)‡-	9 (7, 13)	10 (6, 14)‡	10 (8, 14)	9 (6, 13)‡
Cardiogenic shock, n (%)	68 (1.6)	382 (6.3)‡	54 (3.6)	267 (15.6)‡	14 (0.5)	115 (2.6)‡
New onset HF, n (%)	316 (7.5)	1326 (21.9)‡	193 (12.9)	869 (50.7)‡	123 (4.6)	457 (10.5)‡
Recurrent ischemia, n (%)	99 (2.4)	310 (5.1)‡	44 (2.9)	168 (9.8)‡	255 (2.0)	142 (3.3)‡
Re-infarction, n (%)	18 (0.4)	45 (0.7)†	9 (0.6)	24 (1.4)†	9 (0.3)	21 (0.5)
Stroke, n (%)	9 (0.2)	63 (1.0)‡	4 (0.3)	26 (1.5)†	5 (0.2)	37 (0.9)‡
Major bleeding, n (%)	20 (0.5)	51 (0.8)†	8 (0.5)	24 (1.4)‡	12 (0.4)	27 (0.6)
Death, n (%)	59 (1.4)	543 (9.0)‡	32 (2.1)	295 (17.2)‡	27 (1.0)	248 (5.7)‡
MACCE, n (%)	80 (1.9)	610 (10.1)‡	43 (2.9)	319 (18.6)‡	37 (1.4)	291 (6.7)‡

Compared with patients with revascularization, † $P \ll .05$; ‡ $P \ll .001$; +: revascularization; -: no revascularization; LOS: length of stay; HF: heart failure; MACCE: major adverse cardio-cerebrovascular event.

staff in lower-level hospitals directly resulted in the limited number of CAG/PCI procedures. Although patients' transfer to higher-level hospitals offered a chance of receiving a CAG or revascularization, the already overloaded medical service system in big cities of China had very limited capacity. It calls for greater efforts by Chinese government to carry out more practical policy favoring reassignment of medical investments and skilled practitioners to the less developed districts. increasing reimbursement and physician compensation in such districts.

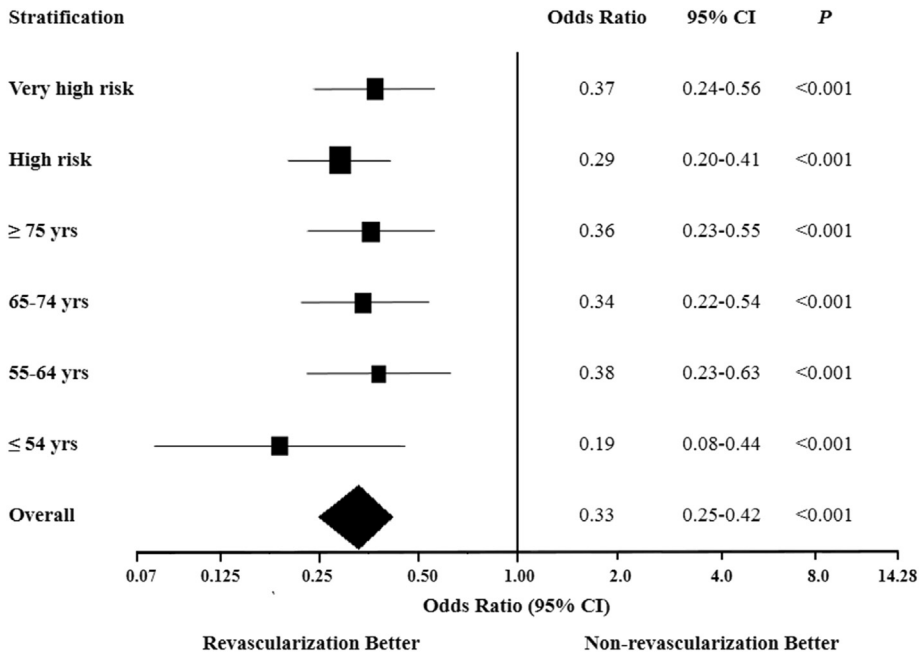
The low rate of CABG in patients with NSTEMI in the present study is mainly due to the lagging behind of development of CAGB in China. Up to 2013, there are only approximately 750 cardiac surgery centers across China, and CABG was carried out in about 55% of those centers. Emergent CABG could only be performed in the few big centers.[30] Additionally, there were obvious differences in proportion of CABG facilities among provincial-level, prefectural-level, and country-level hospitals which were 97.1%(33/34)67.4%(3l/46)and 11.4% (4/35) in CAMI registry.[31] Patients in lower level hospitals could barely have the option of CABG unless they could be transferred to higher level hospitals.

Besides the underuse of revascularization, our study also demonstrated a significantly deferred pattern of revascularization for NSTEMI patients of all ages in China, especially for those who were initially stabilized. The extensive deferral of invasive management even diminished the difference in timing of invasive management between patients with or without transfer, and prolonged the LOS. The unique deferred pattern of revascularization for NSTEMI patients in China revealed by the present study did not match any international guidelines and seemed lacking rationale. Withholding revascularization in older and very-high-risk patients may be justified by their higher burden of comorbidities, shorter life expectancy, and higher risk of invasive procedure associated complications. Yet further investigation is still needed to ascertain the reason why Chinese doctors were reluctant to perform an index PCI or CABG in younger patients or those who were initially stabilized. There were several underlying factors that could possibly hinder timely revascularization in China and might present opportunities for improvement. First, ischemic induced invasive strategy has been applied predominantly in China for decades, and there was barely any robust relevant evidence of early revascularization oriented to Chinese race. It's of great concern that profiles of both thrombophilia and bleeding of Chinese patients may differ greatly from that of western countries,[32] and the risk of early revascularization may therefore outweigh its benefit. Second, mistrust between patient and physician has been growing and become an important factor influencing Chinese practitioner's determination. Doctors in China tend to avoid aggressive strategies in order to lower the risk of iatrogenic adverse events.[33] Third, current costs of hospital bedding in China is relatively low, accounting for only a tiny proportion of total in-hospital expenses. Thus, little increased costs due to prolonged hospital stay allow patients to prefer a conservative or deferred strategy.

Despite increased risk of procedure-related bleeding, patients with revascularization had fewer major bleeding complications in the present study. It may be partly explained by the fact that patients who underwent an invasive procedure were strictly selected, and those with high baseline bleeding risk were mostly excluded from invasive strategy. Under such circumstances, the increased bleeding risk with antithrombotic treatment in patients treated conservatively may even outweigh the total bleeding risk in those treated invasively, especially in the era that transradial approach is predominantly used in China. the LOS of

Age stratification							
≤54 years (n = 2233)		55–64 years (n = 2676)		65–74 years (n = 2906)		≥75 years (n = 2451)	
+ (n = 1200)	- (n = 1033)	+ (n = 1311)	- (n = 1365)	+ (n = 1138)	- (n = 1768)	+ (n = 551)	- (n = 1900)
9 (7, 13)	8 (5, 12)‡	10 (7, 13)	9 (6, 13)‡	11 (8, 14)	9 (6, 14)‡	11 (8, 15)	10 (6, 14)‡
12 (1.0)	37 (3.6)‡	19 (1.4)	56 (4.1)‡	23 (3.0)	101 (5.7)‡	14 (2.5)	188 (9.9)‡
47 (3.9)	104 (10.1)‡	80 (6.1)	219 (16.0)‡	116 (10.2)	404 (22.9)‡	73 (13.2)	599 (31.5)‡
16 (1.3)	30 (2.9)‡	31 (2.4)	48 (3.5)	34 (3.0)	92 (5.2)‡	18 (3.3)	140 (7.4)‡
2 (0.2)	4 (0.4)	8 (0.6)	5 (0.4)	3 (0.3)	15 (0.8)†	5 (0.9)	21 (1.1)
0 (0.0)	2 (0.2)	2 (0.2)	12 (0.9)†	3 (0.3)	20 (1.1)†	4 (0.7)	29 (1.5)
3 (0.3)	2 (0.2)	3 (0.2)	8 (0.6)†	8 (0.7)	15 (0.8)	6 (1.1)	26 (1.4)
5 (0.4)	48 (4.6)‡	15 (1.1)	72 (5.3)‡	20 (1.8)	152 (8.6)‡	19 (3.4)	271 (14.3)‡
7 (0.6)	52 (5.0)‡	23 (1.8)	88 (6.4)‡	25 (2.2)	173 (9.8)‡	25 (4.5)	297 (15.6)‡

Figure 3



Forest Plot of Odds Ratio for in-hospital MACCE in patients of different risk and age stratifications. Patients were stratified very high risk when presented hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure, or recurrent dynamic ST-T wave changes, particularly with

NSTEMI patients (10 days) was twice that reported in United States (4.8 days).[22] The extensive and profound deferral of revascularization might be the major cause of prolonging patients' hospital stay prior to catheterization. Promoting an earlier revascularization strategy as guideline recommended may have an immediate effect of shortening LOS of NSTEMI patients in China.

Limitation

Some limitations of the present study should be acknowledged. First, our study was unavoidably affected by confounding factors such as differences of drug indication, collection of non-randomized data, and missing information. Although a multivariable regression model was introduced in the present study, there might still be some unobserved

Table VI. Baseline characteristics of patients with NSTEMI in CAMI compared with other registries

	CAMI	MINAP/NICOR	SWEDEHEART/RIKS-HIA	ACTION/NCDR	KAMI
Number of patients	10,266	137,009	45,069	147,438	17,464
Region	Mainland China	UK	Swede	US	South Korea
Participating hospitals	107	236	74	500	45
Time span	2013-2016	2007-2010	2007-2010	2007-2010	2006-2013
Age (years)*FIGURE	67.7	73.0	73.0	67.0	66.5
Female (%)	31.7	37.5	37.6	38.7	32.8
Current smoker (%)	35.3	23.0	19.6	29.6	39.8
Diabetes (%)	23.8	21.7	25.0	35.4	33.8
Hypertension (%)	58.5	53.1	50.6	76.3	58.4

CAMI, China acute Myocardial Infarction registry; MINAP/NICOR, The Myocardial Ischemia National Audit Project /National Institute for Cardiovascular Outcomes Research; SWEDEHEART/RIKS-HIA, the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies/ Register of Information and Knowledge About Swedish Heart Intensive Care Admissions; ACTION/NCDR, The Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines/National Cardiovascular Data Registry; KAMI, Korea Acute Myocardial Infarction Registry.
*Mean or median age.

confounders which would have influenced our results, and this research reveals important associations but cannot prove causation. Second, the in-hospital cohort could not completely represent the total NSTEMI population for the relatively small proportion of NSTEMI in CAMI registry, further extension of our findings to the community or countries outside of China should be cautious. Third, some key information, like the preference and the financial status of the patients and their family, reimbursement and physician compensation were unavailable in detail but they are usually very important in Chinese culture. Thus we were unable to completely reveal the underlying factors which might hamper the doctors to initiate an invasive strategy. Finally, only in-hospital outcomes were assessed in the present study. Longer-term outcomes of NSTEMI patients are in great need to justify the unique Chinese pattern of revascularization for these patients.

Conclusions

In the era of early intervention, invasive management was underused and profoundly deferred in patients with NSTEMI across mainland China, especially in those with higher risk profile like female and older patients. Revascularization was associated with lower in-hospital MACCE. Efforts should be made to distinguish more higher-risk patients as candidates for invasive management, to encourage routine early CAG, and to enforce the development of lower level hospitals.

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Disclosures

The authors have no conflicts of interest to disclose. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

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