Early Guideline-Directed Medical Therapy and in-Hospital Major Bleeding Risk in ST-Elevation Myocardial Infarction Patients Treated with Percutaneous Coronary Intervention: Findings from the CCC-ACS Project

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Abstract

Purpose Previous reports demonstrated a bleeding avoidance potential of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and β-blocker. It remains unclear whether early guideline-directed medical therapy [GDMT, i.e., the combined use of β-blocker, angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and statin] confers protection against bleeding in the setting of high-intensity antithrombotic therapy.

Methods We assessed associations between the use of early (within the first 24 h) GDMT and in-hospital major bleeds, ischemic events and mortality among ST-elevation myocardial infarction (STEMI) patients treated with percutaneous coronary intervention (PCI) in the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome project.

Results Among 34,538 STEMI patients without contra-indications to GDMT and eligible for analysis, 35.5% received early GDMT. In a 1-to-2 propensity-score matched cohort, compared with non-early GDMT, early GDMT was associated with a 25% reduction in major bleeds [odds ratio (OR) 0.75, 95% confidence interval (CI) 0.60–0.94], with parallel reductions in ischemic events (OR 0.60, 95%CI 0.45–0.78) and in-hospital mortality (OR 0.43, 95%CI 0.31–0.61). Early GDMT-associated reduction in major bleeds was generally consistently observed across different major bleeding definitions and in sensitivity analyses. Additionally, no significant interaction was observed in subgroup analyses.

Conclusion In a large nationwide registry, early initiation of GDMT was associated with reduced risk for in-hospital major bleeds in STEMI patients treated with PCI. To improve the outcome of STEMI, further effort should be made to reinforce the early use of GDMT in this patient population.

Keywords Guideline-directed medical therapy · ST-elevation myocardial infarction · Percutaneous coronary intervention · Bleeding

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What is Known

- Among stable and unstable coronary syndrome patients, STEMI patients had the highest risk of post-PCI bleeding due to concomitant administration of high-intensity antithrombotic medications in short duration.
- ACEI/ARB and β-blocker, as the key component of GDMT, was demonstrated separately to have protective association against bleeding complications.

What the Study Adds

- Paralleled with reductions in ischemic events and inhospital mortality, early initiation of GDMT (within the first 24 h) was associated with a 25% reduction in major bleeding risk among STEMI patients treated with PCI.
- To improve the outcome of STEMI, further effort should be made to reinforce the early use of GDMT in this patient population.

Methods

Study Design and Population

The CCC-ACS project is an ongoing nationwide registry jointly initiated by the American Heart Association and the Chinese Society of Cardiology from 2014, aiming to improve the quality of care for ACS patients in China. Detailed information on the study design and methodology has been published previously [11]. The CCC-ACS project was approved by the institutional review board of Beijing Anzhen Hospital, Capital Medical University, with a waiver for informed consent. This study is registered at the following URL: https://clinicaltrial.gov (unique identifier: NCT02306616).

In the present analysis, we included STEMI patients who underwent PCI during hospitalization and had no GDMT contraindications. Because all patients in the present study received background dual antiplatelet therapy (DAPT) within the first 24 h, which was included in GDMT for STEMI patients who underwent PCI, the early GDMT was defined as the combination of any dose of the following three medications within 24 h of STEMI onset: ACEI/ARB, β-blocker, and statin. Non-early GDMT was defined as at least one GDMT component was not used within 24 h of STEMI onset. The dosing of DAPT was used for covariate adjustment and propensity score matching (see below). Contraindications to statin included: active liver disease; persistent transaminase elevation of unknown cause; hypersensitivity to statin, myositis, myalgia, and rhabdomyolysis. Contraindications to β-blocker include: cardiogenic shock or unstable decompensated heart failure; sick-sinus syndrome (providing no permanent pacemaker), atrioventricular block of second and third degree; symptomatic bradycardia; hypotension and asthma. Contraindications to ACEI/ARB include: anuria renal failure, heart failure, atrial fibrillation, renal failure, ischemic.

Study Covariates

The following variables were treated as covariates for multivariable adjustment and propensity score matching: demographics (age, sex), previous history (hypertension, diabetes, dyslipidemia, smoking, MI, PCI, coronary artery bypass grafting, heart failure, atrial fibrillation, renal failure, ischemic.
stroke, hemorrhagic stroke, chronic obstructive pulmonary disease, peripheral vascular disease), on-admission clinical characteristics [peak levels of creatine kinase MB (CKMB) isoform, Killip class, serum levels of low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG), levels of systolic and diastolic blood pressure (SBP and DBP), heart rate, estimated glomerular filtration rate (eGFR), and baseline hemoglobin], prehospital medications (pre-hospital thrombolysis, aspirin, P2Y12 inhibitors, statins, β-blockers, ACEIs/ARBs, aldosterone antagonists and oral anticoagulants], in-hospital medications [dual antiplatelet therapy (DAPT) status, aldosterone antagonists, oral anticoagulants, glycoprotein IIb/IIIa inhibitors, and perioperative anticoagulants (unfractionated heparin, low molecular weight heparin (LMWH), and others)] and PCI-related characteristics [time from symptom onset to admission, PCI types (primary PCI <12 h after symptom onset, primary PCI ≥12 h after symptom onset, rescue PCI, and elective PCI) and radial route for PCI or not. eGFR was calculated according to the equation by Chronic Kidney Disease Epidemiology Collaboration [12]. The status of DAPT within the first 24 h was defined as the following three categories: non-loading DAPT (DAPT was not in loading dose), single-loading DAPT (one of DAPT in loading dose), and both-loading DAPT (DAPT both in loading dose). The loading dose of aspirin was defined as ≥150 mg. The loading dose of P2Y12 receptor inhibitor was defined as ≥300 mg for clopidogrel and ≥180 mg for ticagrelor. Primary PCI was defined as emergent PCI with balloon, stent, or other approved device, performed on the infarct-related artery without previous fibrinolytic treatment; rescue PCI was defined as emergent PCI performed as soon as possible in the case of failed thrombolysis, and elective PCI was defined as PCI performed in stable, successful reperfusion for STEMI, or completed infarction post-STEMI. The definition of the above study variables is listed in Supplemental Table 1. For variables with missing values, we imputed the missing data using the sequential regression multiple imputation method by IVEware (version 0.2; Survey Research Center, University of Michigan, Ann Arbor, MI), as previously described [13]. The missing rates of the study variables are shown in Supplemental Table 2. It should be noted that, for BMI, the imputation was not performed due to a high missing rate (>25%). Therefore, in the total population (pre-matched), BMI was not included as a covariable in the propensity-score matched algorithm, and BMI-related subgroup analysis is not based on the full data set.

**Study Outcomes**

The CCC-ACS project routinely collected information concerning bleeding data as a part of in-hospital outcomes, which included: fatal bleeding, hemorrhagic stroke, bleeding in vital organs/locations (intracranial, spinal canal, retropertioneal, pericardial, and intra-ocular with compromised vision), bleeding requiring clinical intervention (requiring pressors, surgery or intravenous vasoactive agents), hemoglobin drop related to bleed (the admission level minus the nadir level), and bleeding requiring blood transfusion and total amount of transfusion. Based on this information, we defined a composite of major bleeds using the following three major bleeding definitions: (1) Bleeding Academic Research Consortium (BARC) type 3b–3c and type 5, which is defined as a hemoglobin drop of ≥5 g/dL or cardiac tamponade or bleeding requiring surgical intervention or bleeding requiring intravenous vasoactive agents (type 3b), intracranial hemorrhage (type 3c), or fatal bleeding (type 5), respectively [14]; (2) Thrombolysis In Myocardial Infarction (TIMI) major bleeding, which is defined as intracranial hemorrhage or clinically overt bleeding associated with a hemoglobin drop of ≥5 g/dL, or fatal bleeding [15]; (3) PLATElet inhibition and patient Outcomes (PLATO) life threatening bleeding, which is defined as fatal bleeding, intracranial bleeding, intraoperative bleeding with cardiac tamponade, severe hypotension, hypovolemic shock due to bleeding and requiring either vasopressor or surgery, a hemoglobin drop of ≥5 g/dL, or the need for transfusion >4 U of whole blood or packed red blood cells [16]. Coronary artery bypass grafting related bleeding was excluded.

We also examined the association between early GDMT status and ischemic events and all cause in-hospital mortality. Ischemic events were defined as the occurrence of re-infarction, in-stent thrombosis (angiographically confirmed) and ischemic stroke.

**Statistical Analysis**

Continuous data with normal distribution are presented as means and standard deviations. Nonparametric continuous data are presented as medians with interquartile ranges and categorical data are presented as number and percentage. We used propensity score matching to balance the differences in patient demographics, medical history and pre-admission and in-hospital management strategies between those received early GDMT and non-early GDMT. We developed a non-parsimonious multivariable logistic regression model to estimate a propensity score for early GDMT status (yes/no) as the dependent variable. The absolute standardized difference (ASD) is recommended to compare baseline covariates. ASD is superior to rank-sum test or t-test since it is independent of sample size, and between-group imbalances were considered to be ideal if it was less than 10% [17] (Stata command “stddiff”). Then, a propensity score matching a maximal ratio of 1-to-2 (Matching cohort 1, Supplemental Table 3), without replacement, with a caliper width of 0.02 was performed (Stata command “calipmatch”). The risk of in-hospital...
bleeding, ischemic events, and mortality in the matched groups was assessed using a logistic regression model on the matched pairs.

We performed the following interaction tests and subgroup analyses based on matched population, including age (<65 years and ≥ 65 years), sex, BMI (a BMI cutoff value of <24 kg/m² was used to define the normal range for the Chinese adults [18]), eGFR (<60 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m²), Killip class (>Class I vs. Class I), and high-intensity antithrombotic therapy (full loading dose DAPT + glycoprotein IIb/IIIa inhibitor + post-PCI anticoagulation).

Finally, we performed the following sensitivity analyses based on the matching cohort 1: (1) excluding patients who died within 48 h of admission; (2) excluding patients with Killip class IV; (3) excluding patients receiving unfractionated heparin; (4) excluding hemorrhagic stroke patients. Additionally, a propensity score with a maximal matching ratio of 1-to-3 (Matching cohort 2, Supplemental Table 3), and another propensity score with a maximal matching ratio of 1-to-2 among patients not receiving DAPT with both in loading doses (Matching cohort 3, Supplemental Table 3), and inverse probability weighting based on multivariate logistic regression (Stata command “teffects ipw”) were used as sensitivity analysis to validate the primary findings. We used Stata version 15.1 (StataCorp, College Station, TX) for analysis. A two-tailed $P < 0.05$ was considered statistically significant.

**Results**

**Patient Characteristics**

From November 2014 to July 2019, 104,516 ACS patients were enrolled in the CCC-ACS project. As shown in Fig. 1, a total of 34,538 patients were included in the final analytic sample, after excluding those admitted with a diagnosis of non-ST-elevation myocardial infarction, those who were not treated with PCI, those with missing value for time from symptom-onset to admission, and those with contraindications to GDMT components. Among them, there were 12,262 patients on early GDMT and 22,276 patients on non-early GDMT. As shown in Supplemental Table 4, compared with patients on non-early GDMT, patients on early GDMT were more likely to have high levels of admission levels of
## Table 1 Baseline characteristics between patients who received early GDMT v.s. non-early GDMT after propensity score matching

| Characteristics | Total no. of patients | Early GDMT | Non-early GDMT | ASD, % |
|-----------------|-----------------------|------------|---------------|--------|
| **n=26,943**    |                       |            |               |        |
| **Early GDMT**  |                       |            |               |        |
| **n=8995**      |                       |            |               |        |
| **Non-early GDMT** |                     |            |               |        |
| **n=17,948**    |                       |            |               |        |
| **ASD, %**      | 16,576 (92.4)         | 5768 (32.1) | 3777 (21.0)   |        |
| **GDMT components** |                   |            |               |        |
| Statin, n (%)   | 25,571 (94.9)         | 8995       | 8995          | 2.70   |
| β-blocker, n (%)| 14,763 (54.8)         | 8995       | 5768 (32.1)   | 0.49   |
| ACEI/ARB, n (%) | 12,772 (47.4)         | 8995       | 3777 (21.0)   |        |
| **Demographics** |                       |            |               |        |
| Age, year       | 60.7±12.2             | 60.4±12.2  | 60.8±12.3     | 0.49   |
| Male, n (%)     | 21,684 (80.5)         | 7251 (80.6)| 14,433 (80.4) |        |
| **Medical history** |                    |            |               |        |
| Smoking, n (%)  | 13,942 (51.8)         | 4672 (51.9)| 9270 (51.7)   | 0.58   |
| Hypertension, n (%)| 12,895 (47.9)       | 4424 (49.2)| 8471 (47.2)   | 3.97   |
| Diabetes, n (%) | 5192 (19.3)           | 1742 (19.4)| 3450 (19.2)   | 0.42   |
| Dyslipidemia, n (%)| 1496 (5.55)          | 503 (5.59) | 993 (5.53)    | 0.37   |
| MI, n (%)       | 1239 (4.60)           | 405 (4.50) | 834 (4.65)    | 0.69   |
| PCI, n (%)      | 1221 (4.53)           | 397 (4.41) | 824 (4.59)    | 0.86   |
| CABG, n (%)     | 43 (0.16)             | 16 (0.18)  | 27 (0.15)     | 0.68   |
| COPD, n (%)     | 249 (0.92)            | 81 (0.90)  | 168 (0.94)    | 0.37   |
| Heart failure, n (%)| 121 (0.45)          | 38 (0.42)  | 83 (0.46)     | 1.67   |
| Renal failure, n (%)| 142 (0.53)          | 46 (0.51)  | 96 (0.53)     | 0.33   |
| Atrial fibrillation, n (%)| 279 (1.04)       | 96 (1.07)  | 183 (1.02)    | 0.47   |
| Ischemic stroke, n (%)| 1607 (5.96)        | 540 (6.00) | 1067 (5.94)   | 0.25   |
| Hemorrhagic stroke, n (%)| 172 (0.64)          | 64 (0.71)  | 108 (0.60)    | 1.36   |
| Peripheral vascular disease, n (%)| 126 (0.47)      | 43 (0.48)  | 83 (0.46)     | 0.23   |
| **Clinical variables** |                      |            |               |        |
| SBP, mmHg       | 128±21.9              | 129±21.0   | 128±22.3      | 6.74   |
| DBP, mmHg       | 78.7±14.0             | 79.3±13.8  | 78.4±14.1     | 6.64   |
| Heart rate, bpm | 78.2±15.5             | 78.5±13.7  | 78.0±16.3     | 3.50   |
| Killip class, n (%) | 20,496 (76.1)    | 6864 (76.3)| 13,632 (76.0)| 2.52   |
| Class I         | 4870 (18.1)           | 1652 (18.4)| 3218 (17.9)   |        |
| Class II        | 849 (3.15)            | 267 (2.97) | 582 (3.24)    |        |
| Class IV        | 728 (2.70)            | 212 (2.36) | 516 (2.87)    |        |
| CK-MB peak, µg/L| 36.4 (11.2–91.9)      | 36.8 (11.8–88.0) | 36.2 (10.9–94.1) | 1.67   |
| LDL-C, mg/dL    | 108 (86.0–132)        | 108 (86.0–131) | 108 (85.0–132) | 0.98   |
| HDL-C, mg/dL    | 41.0 (34.0–49.0)      | 41.0 (34.0–48.0) | 41.0 (34.0–49.0) | 1.61   |
| TG, mg/dL       | 129 (90.0–193)        | 132 (92.0–194) | 127 (89.0–193) | 1.70   |
| eGFR, mL/min/1.73m² | 88.0±21.9           | 88.4±21.3  | 87.8±22.2     | 2.69   |
| Hemoglobin on admission, g/dL | 141 (129–153) | 142 (129–153) | 141 (129–153) | 1.98   |
| **Pre-hospital medications** |                      |            |               |        |
| Pre-hospital thrombolysis, n (%) | 438 (1.63) | 152 (1.69) | 286 (1.59) | 0.76   |
| Aspirin, n (%)  | 3890 (14.4)           | 1294 (14.4)| 2596 (14.5)   | 0.13   |
| P2Y₁₂ inhibitor, n (%)| 3039 (11.3)       | 1013 (11.3)| 2026 (11.3)   | 0.08   |
| Statin, n (%)   | 2489 (9.24)           | 817 (9.08) | 1672 (9.32)   | 0.81   |
| Oral anticoagulants, n (%)| 41 (0.15)           | 13 (0.14)  | 28 (0.16)     | 0.30   |
| β-blocker, n (%) | 1167 (4.33)           | 422 (4.69) | 745 (4.15)    | 2.63   |
| ACEI/ARB, n (%) | 1540 (5.72)           | 559 (6.21) | 981 (5.47)    | 3.19   |
| Aldosterone antagonist, n (%)| 174 (0.65)           | 59 (0.66)  | 115 (0.64)    | 0.19   |
| **In-hospital medications** |                      |            |               |        |
| DAPT status after admission, n (%) | 1.71      |            |               |        |
blood pressure and heart rate, lower levels of admission peak CK-MB and lower Killip class. Moreover, patients on early GDMT were more likely to receive LMWH and aldosterone antagonist. After propensity score matching, a cohort composed of 8995 patients on early GDMT (73.4% of the total early GDMT population) and 17,948 patients on non-early GDMT was constructed, with well-balanced demographics, pre-admission characteristics, medical history, admission characteristics, and in-hospital management strategies. The baseline characteristics of post-matching cohorts are shown in Table 1, and the ASD between pre- and post-matched cohorts are shown in Fig. 2.

**Associations between Early GDMT and Major in-Hospital Bleeds, Ischemic Events and Mortality**

In propensity score-matched cohort, a total of 400 composite major bleeds, 294 ischemic events, and 229 deaths were recorded, with incidence rate of 1.48%, 1.09%, and 0.85%, respectively. Compared with non-early GDMT, early GDMT was associated with a 25% reduction in major bleeds [odds ratio (OR) 0.75, 95% confidence interval (CI) 0.60–0.94], a 40% reduction in ischemic events (OR 0.60, 95%CI 0.45–0.78), and a 57% reduction in mortality (OR 0.43, 95%CI 0.31–0.61). Notably, early GDMT-associated reduction in bleeding risk was generally consistent for BARC- (OR 0.80, 95%CI 0.64–1.00), TIMI- (OR 0.68, 95%CI 0.52–0.90), and PLATO- (OR 0.73, 95%CI 0.58–0.93) defined major bleeds (Fig. 3). Moreover, as shown in Fig. 4, the reduction in major bleeding risk was consistent across subgroups, and no significant interaction was observed among subgroups.

**Sensitivity Analysis**

As shown in Fig. 5, the sensitivity analyses based on a 1-to-2 matched cohort (Matching cohort 1) revealed that the protective association of early GDMT against major bleeds remained statistically significant after excluding patients who died within 48 h of admission, patients with Killip class IV, patients receiving unfractionated heparin, and hemorrhagic stroke patients. Additional sensitivity analyses based on a 1-to-3 matched cohort (Matching cohort 2; covariate balance after matching was shown

| Table 1 (continued) |
|---------------------|
| Characteristics     | Total no. of patients | Early GDMT | Non-early GDMT | ASD, % |
|---------------------|
| DAPT was not in loading dose | 1220 (4.53) | 235 (2.61) | 985 (5.49) | 0.39 |
| One of DAPT in loading dose | 7944 (29.5) | 2939 (33.7) | 5005 (27.9) | 0.06 |
| DAPT both in loading dose | 17,779 (66.0) | 5821 (64.7) | 11,958 (66.6) | 0.35 |
| Anticoagulation therapy, n (%) | | | | |
| Unfractionated heparin | 1264 (4.69) | 417 (4.64) | 847 (4.72) | 0.39 |
| LMWH | 19,378 (71.9) | 2575 (72.8) | 12,828 (71.5) | 0.06 |
| Others | 822 (3.05) | 275 (3.06) | 547 (3.05) | 0.06 |
| Oral anticoagulants, n (%) | 121 (0.45) | 39 (0.43) | 82 (0.46) | 0.35 |
| Aldosterone antagonist, n (%) | 4408 (16.4) | 1540 (17.1) | 2868 (16.0) | 3.07 |
| Glycoprotein IIb/IIIa inhibitor, n (%) | 11,615 (43.1) | 3876 (43.1) | 7739 (43.1) | 0.06 |
| PCI related | | | | |
| Time from symptom-onset to hospital admission, n (%) | | | | 0.18 |
| <6 h | 14,365 (53.3) | 4797 (53.3) | 9568 (53.3) | 0.39 |
| 6–12 h | 5062 (18.8) | 1688 (18.8) | 3374 (18.8) | 0.39 |
| 12–24 h | 2592 (9.62) | 853 (9.48) | 1739 (9.69) | 0.39 |
| >24 h | 4924 (18.3) | 1657 (18.4) | 3267 (18.2) | 0.39 |
| Radial route for PCI, n (%) | 25,435 (94.4) | 8489 (94.4) | 16,946 (94.4) | 0.19 |
| PCI type, n (%) | | | | 0.15 |
| Primary, <12 h | 18,203 (67.6) | 6086 (67.7) | 12,117 (67.5) | 0.39 |
| Primary, ≥12 h | 2502 (9.29) | 820 (9.12) | 1682 (9.37) | 0.39 |
| Rescue | 350 (1.30) | 110 (1.22) | 240 (1.34) | 0.39 |
| Elective | 5888 (21.9) | 1979 (22.0) | 3909 (21.8) | 0.39 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CK-MB, creatine kinase MB isoform; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TG, triglycerides
in Supplemental Table 5 and Supplemental Fig. 2), revealed that early GDMT-associated reduction in major bleeds (OR 0.68, 95% CI 0.53–0.87) was consistent for composite bleeds, as well as for BARC- (OR 0.74, 95% CI 0.58–0.96), TIMI- (OR 0.67, 95% CI 0.50–0.91), and PLATO-defined major bleeds (OR 0.65, 95% CI 0.50–0.85). Moreover, early GDMT was associated with similar magnitude of reductions in ischemic events (OR 0.56, 95% CI 0.44–0.71).
0.42–0.75) and in-hospital mortality (OR 0.42, 95%CI 0.30–0.60) as observed in the matching cohort 1. The results based on propensity score with a maximal matching ratio of 1-to-2 among patients not receiving DAPT with both in loading doses (Matching cohort 3; covariate balance before and after matching was shown in Supplemental Table 6, Supplemental Table 7, Supplemental Fig. 3, and the results in detail was shown in Supplemental Fig. 4) and inverse probability weighting algorithm also confirmed the above findings (Supplemental Fig. 5).

### Discussion

In a large nationwide registry in China, we showed that early initiation of GDMT, i.e., the combined use of statin, β-blocker, and ACEI/ARB within the first 24 h, was associated with a 25% reduction in major bleeding risk among STEMI patients treated with PCI. This finding was consistent according to all methods used (propensity score matching and inverse probability weighting). Although the efficacy of GDMT in reducing in-hospital ischemic events and mortality in STEMI has been well documented, to our knowledge, our work for the first time demonstrated a protective association between early GDMT and bleeding risk in this patient population. Notably, in the present study, 0.5% of patients (1824/36362, shown in Fig. 1) had a clear contraindication to GDMT, whereas only 35.5% (12,262/34,538) of patients without a clear contraindication received GDMT within the first 24 h. This clearly indicates a large evidence-to-practice gap. Based on our findings, early GDMT should be further strengthened in STEMI patients, in terms of its potential benefit as a novel bleeding avoidance strategy, in addition to its proved efficacy in the secondary prevention of ASCVD.

| Total | Early GDMT | Non-Early GDMT | Odds Ratios for Major Bleeding Risk and 95% Confidence Interval |
|-------|------------|----------------|---------------------------------------------------------------|
| n=26943 | n=8995 | n=17948 | Favors Early GDMT | Favors Non-Early GDMT |
| **Age ≥ 65 years** | | | | |
| Yes | 10241 (38.0) | 3355 (37.3) | 6886 (38.4) | |
| No | 16702 (62.0) | 5640 (62.7) | 11062 (61.6) | 0.72 (0.51 to 1.00) |
| **Sex** | | | | 0.79 (0.59 to 1.06) |
| Male | 21794 (80.9) | 7251 (80.6) | 14433 (80.4) | |
| Female | 5284 (19.6) | 1744 (19.4) | 3515 (19.6) | 0.73 (0.56 to 0.94) |
| **BMI ≥ 24 kg/m²** | | | 0.84 (0.54 to 1.31) |
| Yes | 9098 (54.6) | 3027 (57.3) | 6071 (53.4) | 0.79 (0.52 to 1.19) |
| No | 7564 (45.4) | 2258 (42.7) | 5306 (46.6) | 0.74 (0.48 to 1.13) |
| **eGFR < 60 mL/min/1.73m²** | | | 0.815 |
| Yes | 3165 (11.8) | 996 (11.1) | 2169 (12.1) | 0.79 (0.52 to 1.19) |
| No | 23778 (88.2) | 7999 (88.9) | 15779 (87.9) | 0.74 (0.48 to 1.13) |
| **Killip Class > Class l** | | | |
| Yes | 6447 (23.9) | 2131 (23.7) | 4316 (24.1) | |
| No | 20496 (76.1) | 6864 (76.3) | 13632 (76.0) | 0.73 (0.51 to 1.06) |
| **Full Loading Dose DAPT + Glycoprotein IIb/IIa inhibitor + Heparin/LMWH/Others** | | | |
| Yes | 6984 (25.9) | 2252 (25.0) | 4732 (26.4) | |
| No | 19959 (74.1) | 6743 (75.0) | 13216 (73.6) | 0.73 (0.56 to 0.96) |

*BMI was derived from 16,662 participants without missing value. Abbreviations: BMI, body mass index; DAPT, dual anti-platelet therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy.*

0.42–0.75 and in-hospital mortality (OR 0.42, 95%CI 0.30–0.60) as observed in the matching cohort 1. The results based on propensity score with a maximal matching ratio of 1-to-2 among patients not receiving DAPT with both in loading doses (Matching cohort 3; covariate balance before and after matching was shown in Supplemental Table 6, Supplemental Table 7, Supplemental Fig. 3, and the results in detail was shown in Supplemental Fig. 4) and inverse probability weighting algorithm also confirmed the above findings (Supplemental Fig. 5).
Across different clinical presentations (chronic and acute coronary syndromes) indicated for PCI, due to the concomitant administration of high-intensity antiplatelet and anticoagulant medications in short duration, STEMI patients had the highest risk of post-PCI bleeding [19], which would be more likely to occur during hospitalization following PCI [20], and independently predicted mortality after STEMI [21]. Current measures to reduce bleeding risk in this clinical scenario remain insufficient. Given the previous reports concerning the bleeding avoidance potential of the individual component of GDMT, especially β-blockers and ACEI/ARB, the potential of early GDMT to reduce bleeding risk and its clinical value need to be reassessed. To the best of our knowledge, the present study is the first attempt to evaluate the association between early GDMT and bleeding risk STEMI during hospitalization. Bleeding complications after PCI is generally categorized as procedure-related bleeding that usually occurs within 7 days and during hospitalization, and non-procedure related bleeding, also called spontaneous bleedings that occurs from 7 days after discharge [22]. In this regard, our findings provide the first evidence that early GDMT was associated with reduced risk for procedure-related bleeding in STEMI patients.

|                          | Total | Early GDMT | Non-Early GDMT | Odds Ratios for Major Bleeding Risk and 95% Confidence Interval | P     |
|--------------------------|-------|------------|----------------|---------------------------------------------------------------|-------|
| **Total Effects (In Matching Cohort 1)** |       |            |                |                                                               |       |
| Total Effects (In Matching Cohort 2) |       |            |                |                                                               |       |
| Total Effects (In Matching Cohort 3) |       |            |                |                                                               |       |
| Total Effects (By Inverse Probability Weighting In Matching Cohort 1) |       |            |                |                                                               |       |
| Excluding Patients Died Within 48 Hours of Admission In Matching Cohort 1 |       |            |                |                                                               |       |
| Excluding Patients With Killip Class IV In Matching Cohort 1 |       |            |                |                                                               |       |
| Excluding Patients Receiving Unfractionated Heparin In Matching Cohort 1 |       |            |                |                                                               |       |
| Excluding Hemorrhagic Stroke Patients In Matching Cohort 1 |       |            |                |                                                               |       |
| 346/26868 (1.29) | 97/8974 (1.08) | 249/17894 (1.39) | 0.77 (0.61 to 0.98) | 0.034 |

**Fig. 5** Sensitivity analysis. *Matching cohort 1: Detailed matching information is shown in Table 1 and Fig. 2. †Matching cohort 2: Detailed matching information is shown in Supplemental Table 5 and Supplemental Fig. 1. §Matching cohort 3: Detailed matching information is shown in Supplemental Table 7 and Supplemental Fig. 3. Abbreviations: DAPT, dual anti-platelet therapy; GDMT, guideline-directed medical therapy.

Notably, recent evidence also supports a protective association between GDMT and non-procedure related bleeding following PCI. A post-hoc analysis of the Dual Antiplatelet Therapy (DART) study evaluated the impact of optimal medical therapy (OMT; an equivalent term to GDMT) on cardiovascular outcomes in patients who underwent PCI with drug-eluting stent and completed 1 year of DAPT during an additional 18 months of continued use of clopidogrel or prasugrel [23]. The patients included in the DAPT study were free of major adverse cardiovascular or cerebrovascular event, repeat revascularization or global use of strategies to open occluded arteries (GUSTO) moderate or severe bleeding at 12 months. During an additional 18 months of P2Y12 inhibition, 63% patients were on OMT. After multivariable adjustment, the use of OMT was associated with a 30% reduction in GUSTO moderate or severe bleeding (hazard ratio, 0.70; 95% CI 0.52–0.93) during 12 to 30 months following PCI. Taken together, the findings from our study and the post-hoc analysis of DAPT study, clearly identified a GDMT-associated reduction in bleeding risk both during hospitalization and post-discharge. In our study, after excluding patients with clear contraindications to GDMT, the prescribing rate for GDMT within the first 24 h was only 35.5%. This percentage is significantly lower than that reported by the PROMETHEUS Registry (69.4%) [24]. Given the clinical benefits of early
GDIMT presented in the present study, specific efforts should be made in the future to address the underuse of GDIMT in clinical practice in China.

Due to the proved clinical efficacy in the secondary prevention of ASCVD, GDIMT is currently recognized as the background treatment for STEMI patients. Therefore, it is difficult to establish a causal relationship between GDIMT and its bleeding avoidance potential in randomized controlled trials. Currently, scattered evidence exists supporting the bleeding reduction potential for individual components of GDIMT. For example, animal experiments have confirmed that ACEI/ARB is capable of maintaining gastric blood flow, inhibiting the inflammatory response caused by stress response, and protects the gastric mucosa from the impact of stress ulcer, thereby reducing gastrointestinal bleeding [25, 26]. Recent clinical observation also suggests that ACEIs/ARBs were associated with lower risk of major gastrointestinal bleeds in continuous-flow left ventricular assist device patients, which may be due to the prevention of arteriovenous malformations formation [10]. With regard to β-blockers, accumulating evidence suggests that propranolol has a role in reducing the incidence of the first episode of upper gastrointestinal bleeding in patients with cirrhosis, with significant survival benefits. Therefore, non-selective β-blockers have been recommended for primary and secondary prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices [9]. Collectively, the available evidence of the main components of GDIMT, provides pharmacological evidence that early GDIMT would exert a synergistic effect on the reduced bleeding risk among STEMI patients treated with PCI.

Our study has the following limitations. First, as an observational study, we cannot establish a causal relationship between early GDIMT and major bleeding risk. Second, although we use propensity score matching to minimize bias, we cannot exclude the impact of unmeasured confounders. For example, the absence of information concerning cancer disease could be a limitation of this study. Cancers that are diagnosed within the previous 12 months or ongoing active cancer treatment are associated with higher rates of inpatient bleeding [3]. Third, considering clinically important differences in thrombogenicity and propensity for bleeding complications might exist between ethnic groups [27], our findings should not be overgeneralized. Fourth, our cohort was primarily composed of male patients, the generalizability of this finding to females needs further validation. Based on our finding, although an attenuation of treatment effect size associated with early GDIMT in terms of major bleeding risk was observed among female patients (Fig. 4), which could be explained by the fact that female sex was an established risk factor for bleeding following PCI, early GDIMT was indeed associated with an obvious reduction in in-hospital mortality among females (Supplemental Fig. 6). Therefore, early GDIMT should be further encouraged in female patients.

In a large nationwide registry in China, among STEMI patients treated with PCI, in parallel with reductions in ischemic events and in-hospital mortality, we demonstrated a protective association between early initiation of GDIMT, i.e., the combined use of β-blocker, ACEI/ARB, and statin within the first 24 h, and reduced risk for in-hospital major bleeds. To improve the clinical care of STEMI in the Chinese population, further effort should be made to reinforce the early use of GDIMT in this patient population.

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Authors’ Contributions The article was written on behalf of the CCC-ACS project investigators. XZ and QY conceived and designed the study, supervised the analysis process, interpreted the data and revised the manuscript. ZL and PY analyzed the data and drafted the manuscript. ZL, PY, GA, HS, HL, XS, ZJ, and LL helped to analyze the data and figure generation. YH, JL, and DZ supervised the CCC-ACS project and edited the data. All authors read and approved the final manuscript.

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Availability of Data and Materials The data and study materials will be made available for onsite audits by third parties for the purposes of reproducing the results or replicating the procedure.

Declarations

Ethics Approval and Consent to Participate The CCC-ACS project was approved by the institutional review board of Beijing Anzhen Hospital, Capital Medical University, with a waiver for informed consent.

Competing Interests The authors declare that no competing interests exist.

Research Involving Human Participants and/or Animals This study involved human participants, with a waiver for informed consent.

Informed Consent Informed consent was waived for this study.

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