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

BACKGROUND

Previous reports demonstrated a bleeding avoidance potential of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and β-blocker. It remains unclear whether 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 hours) 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, early GDMT was associated with a 28% reduction in major bleeds [odds ratio (OR): 0.72, 95% confidence interval (CI): 0.58 to 0.90], with parallel reductions in ischemic events (OR: 0.60, 95% CI: 0.46 to 0.78) and in-hospital mortality (OR: 0.41, 95% CI: 0.30 to 0.57). GDMT-associated reduction in major bleeds was consistently observed across different major bleeding definitions and in sensitivity analyses. Additionally, no significant interaction was observed in subgroup analyses.

CONCLUSIONS

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 use of GDMT in this patient population.

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, were demonstrated separately to have protective association against bleeding complications.

What The Study Adds

- Paralleled with reductions in ischemic events and in-hospital mortality, early initiation of GDMT (within the first 24 hours) was associated with a 28% 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 use of GDMT in this patient population.

Introduction

Attribute to continued improvement of technical and procedural advances, the outcomes of ST-elevation myocardial infarction (STEMI) patients after percutaneous coronary intervention (PCI) has been dramatically improved.[1, 2] Notably, there has been a concomitant increase in bleeding events associated with the use of more potent, longer-duration perioperative antithrombotic therapy in this patient population.[3] In the SWEDEHEART registry, a gradually increased in-hospital bleeding from 0.5% in 1995 to a peak of 2% in 2005/2006 was observed, which was paralleled by an increasing use of PCI and antithrombotic therapy; notably, the implementation of bleeding avoidance strategy was associated with a concomitantly slight decline of bleeding rate to 1.3% in 2007-2010.[4] Given that major bleeding is a costly complication associated with both short-term and long-term adverse outcomes following PCI, existing measures to reduce bleeding remain inadequate.[5]

Early initiation of guideline-directed medical therapy (GDMT), which includes a combined use of statin, β-blocker and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), has been recommended in current guidelines for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) after STEMI.[6–8] Moreover, it's worth noting that recent studies have suggested that individual component of GDMT, such as ACEI/ARB and β-blocker, also had potential in reducing bleeding risk.[9, 10] To our knowledge, the impact of GDMT on the risk of bleeding in eligible patients treated with PCI for STEMI remains unclear.

In the present study, we took advantage of the CCC-ACS project (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome), an ongoing nationwide registry for acute coronary syndrome (ACS) in China, to examine the association between early (within the first 24 hours) GDMT use and major in-hospital bleeding risk among STEMI patients treated with PCI in contemporary practice.

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. GDMT was defined as the combination of the following three medications within 24 hours of STEMI onset: ACEI/ARB, β-blocker and statin. Non-GDMT was defined as at least one GDMT component was not used. Contraindications to statin include: 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 with hyperkalemia, bilateral renal artery stenosis, isolated kidney with renal artery stenosis, pregnant and lactating women.

Study Covariates

The following variables were treated as covariates for multivariable adjustment and propensity score matching: demographics (age, gender), 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), pre-hospital medications (pre-hospital thrombolysis, aspirin, $P2Y_{12}$ 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 hours after symptom onset, primary PCI ≥12 hours after symptom onset, rescue PCI and elective PCI) and radial route for PCI or not. eGFR was calculated according the equation by Chronic Kidney Disease Epidemiology Collaboration.[12] The status of dual antiplatelet therapy (DAPT) within the first 24 hours was defined as the following four categories: non-DAPT (single antiplatelet therapy), 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 $P2Y_{12}$ receptor inhibitor was defined as ≥300 mg for clopidogrel and ≥180 mg for ticagrelor. The definition of the above study variables is listed in **Supplemental Table 1**.

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, retroperitoneal, 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 these 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;[13] (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;[14] (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.[15] Coronary artery bypass grafting related bleeding was excluded.

We also examined the association between 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 GDMT and non-GDMT patients. We developed a non-parsimonious multivariable logistic regression model to estimate a propensity score for GDMT status (yes/no) as the dependent variable. Between-group imbalances were considered to be ideal if the absolute standardized difference (ASD) for a given covariate was less than 10%[16] (Stata command “stddiff”). Then, a propensity score matching of a maximal ratio of 1-to-2, 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.

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.[17] It should be noted that, for BMI, the imputation was not performed due to a high missing rate (>25%). Therefore, BMI-related subgroup analysis and sensitivity analysis are not based on the full data set.

We performed the following interaction tests and subgroup analyses based on matched population, including age (<65 years and ≥65 years), sex, BMI (<28 kg/m^2 and ≥28 kg/m^2), eGFR (<60 mL/min/1.73m^2 and ≥60 mL/min/1.73m^2), DAPT status (full loading or not) and Killip class (>Class I vs. Class I).

Finally, we performed the following sensitivity analyses based on the matching cohort of 1-to-2: (1) excluding patients receiving DAPT with both in loading dose; (2) excluding patients died within 48 hours of admission; (3) excluding patients with Killip Class IV; (4) excluding patients receiving unfractionated heparin; (5) excluding patients who had previous history of hemorrhagic stroke. Additionally, a propensity score-matched with a maximal matching ratio of 1-to-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 January 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 was 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 GDMT patients and 22,276 non-GDMT patients. As shown in **Supplemental Table 2**, compared with non-GDMT patients, GDMT patients were more likely to have high levels of admission levels of blood pressure and heart rate, lower levels of admission peak CK-MB and lower Killip class. Moreover, GDMT patients were more likely to receive LMWH and aldosterone antagonist. After propensity-score matching, a cohort composed of 9,040 GDMT patients (73.7% of the total GDMT population) and 18,038 non-GDMT patients 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.

Table 1
Baseline characteristics between GDMT patients and non-GDMT patients in post-matched cohorts

Characteristics	No. of Patients n = 27078	GDMT n = 9040	Non-GDMT n = 18038	ASD, %
Demographics				
Age, year	60.7 ± 12.2	60.6 ± 12.2	60.7 ± 12.2	0.94
Male, n (%)	21794 (80.5)	7272 (33.4)	14522 (66.6)	0.17
Medical history				
Smoking, n (%)	13942 (51.5)	4640 (33.3)	9302 (66.7)	0.48
Hypertension, n (%)	12978 (47.9)	4457 (34.3)	8521 (65.7)	4.13
Diabetes, n (%)	5233 (19.3)	1757 (33.6)	3476 (66.4)	0.42
Dyslipidemia, n (%)	1485 (5.48)	491 (33.1)	994 (66.9)	0.35
MI, n (%)	1221 (4.51)	403 (33.0)	818 (67.0)	0.37
PCI, n (%)	1201 (4.44)	404 (33.6)	797 (66.4)	0.25
CABG, n (%)	38 (0.14)	12 (31.6)	26 (68.4)	0.31
COPD, n (%)	247 (0.91)	84 (34.0)	163 (66.0)	0.27
Heart failure, n (%)	121 (0.45)	38 (31.4)	83 (68.6)	0.60
Renal failure, n (%)	148 (0.55)	48 (32.4)	100 (67.6)	0.32
Atrial fibrillation, n (%)	293 (1.08)	97 (33.1)	196 (66.9)	0.13
Ischemic stroke, n (%)	1577 (5.82)	530 (33.6)	1047 (66.4)	0.25
Hemorrhagic stroke, n (%)	177 (0.65)	63 (35.6)	114 (64.4)	0.80
Peripheral vascular disease, n (%)	126 (0.47)	46 (36.5)	80 (63.5)	0.95
Clinical variables				
SBP, mmHg	128 ± 21.9	129 ± 20.9	128 ± 22.4	6.81
DBP, mmHg	78.7 ± 13.7	79.3 ± 13.7	78.5 ± 14.2	6.21
Heart rate, bpm	78.2 ± 15.6	78.7 ± 13.9	78.0 ± 16.3	4.14
Killip class, n (%)				1.45
Class □	20469 (75.6)	6871 (33.6)	13598 (66.4)	
Class □	4861 (18.0)	1715 (35.3)	3146 (64.7)	
Class □	889 (3.28)	261 (29.4)	628 (70.6)	

Characteristics	No. of Patients n = 27078	GDMT n = 9040	Non-GDMT n = 18038	ASD, %
Class □	859 (3.17)	193 (22.5)	666 (77.5)	
CK-MB peak, μg/L	36.7 (11.2–93.0)	34.5 (11.8–88.0)	36.8 (10.9–96.2)	2.14
LDL-C, mg/dL	108 (86.0-132)	108 (86.0-132)	108 (85.0-132)	0.67
HDL-C, mg/dL	41.0 (34.0–49.0)	41.0 (34.0–48.0)	41.0 (34.0–49.0)	1.35
TG, mg/dL	129 (90.0-193)	131 (92.0-193)	127 (89.0-193)	0.19
eGFR, mL/min/1.73m^2	88.0 ± 21.8	88.3 ± 21.2	87.8 ± 22.2	2.11
Hemoglobin on admission, g/dL	142 (129–153)	142 (129–153)	141 (129–153)	1.43
Pre-hospital medications				
Pre-hospital thrombolysis, n (%)	429 (1.58)	142 (33.1)	287 (66.9)	0.16
Aspirin, n (%)	3889 (14.4)	1301 (33.5)	2588(66.5)	0.13
P2Y12 inhibitor, n (%)	3047 (11.3)	1003 (32.9)	2044 (67.1)	0.75
Statin, n (%)	2480 (9.16)	799 (32.2)	1681 (67.8)	1.67
Oral anticoagulants, n (%)	45 (0.17)	14 (31.1)	31 (68.9)	0.42
β-blocker, n (%)	1143 (4.22)	406 (35.5)	737 (64.5)	2.00
ACEI/ARB, n (%)	1546 (5.71)	556 (36.0)	990 (64.0)	2.82
Aldosterone antagonist, n (%)	174 (0.64)	53 (30.5)	121 (69.5)	1.07
In-hospital medications				
DAPT status after admission, n (%)				0.30
DAPT was not in loading dose	1235 (4.56)	247 (20.0)	988 (80.0)	
One of DAPT in loading dose	7953 (29.4)	2996 (37.7)	4957 (62.3)	
DAPT both in loading dose	17890 (66.1)	5797 (32.4)	12093 (67.6)	
Anticoagulation therapy, n (%)				
Unfractionated heparin	1286 (4.75)	413 (32.1)	873 (67.9)	1.28

Characteristics	No. of Patients n = 27078	GDMT n = 9040	Non-GDMT n = 18038	ASD, %
LMWH	19447 (71.8)	6585 (33.9)	12862 (66.1)	3.43
Others	818 (3.02)	283 (34.6)	535 (65.4)	0.96
Oral anticoagulants, n (%)	125 (0.46)	40 (32.0)	85 (68.0)	0.43
Aldosterone antagonist, n (%)	4440 (16.4)	1556 (35.1)	2884 (65.0)	3.29
Glycoprotein IIb/IIIa inhibitor, n (%)	11706 (43.2)	3913 (33.4)	7793 (66.6)	0.17
PCI related				
Time from symptom-onset to hospital admission, n (%)				1.29
<6 h	12234 (45.2)	6098 (49.8)	6136 (50.2)	
6–12 h	4296 (15.9)	2108 (49.1)	2188 (50.9)	
12–24 h	2313 (8.54)	1160 (50.2)	1153 (49.8)	
>24 h	4371 (16.1)	2241 (51.3)	2130 (48.7)	
Radial route for PCI, n (%)	25571 (94.4)	8551 (33.4)	17020 (66.6)	1.03
PCI type, n (%)				1.13
Primary, < 12 h	18315 (67.6)	6102 (33.3)	12213 (66.7)	
Primary, ≥ 12 h	2501 (9.24)	819 (32.8)	1682 (67.3)	
Rescue	354 (1.31)	104 (29.4)	250 (70.6)	
Elective	5908 (21.8)	2015 (34.1)	3893 (65.9)	

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.

Associations between GDMT and major in-hospital bleeds, ischemic events and mortality

In propensity score-matched cohort, a total of 404 composite major bleeds, 319 ischemic events, and 255 deaths were recorded, with incidence rate of 1.49%, 1.18%, and 0.94%, respectively. Compared with non-GDMT, GDMT was associated with a 28% reduction in major bleeds [odds ratio (OR) 0.72, 95% confidence interval (CI): 0.58–0.90], a 40% reduction in ischemic events (OR: 0.60, 95%CI: 0.46–0.78) and a 59%

reduction in mortality (OR: 0.41, 95%CI: 0.30–0.57). Notably, GDMT-associated reduction in bleeding risk was consistent for BARC- (OR: 0.77, 95%CI: 0.62–0.97), TIMI- (OR: 0.66, 95%CI: 0.50–0.87), and PLATO- (OR: 0.70, 95%CI: 0.55–0.89) defined major bleeds (Fig. 3). Moreover, as shown in Fig. 4, the reduction in major bleeding risk was generally consistent across subgroups, and no significant interaction was observed among subgroups.

Sensitivity Analysis

As shown in Fig. 5, the sensitivity analyses based on the 1-to-2 matched cohort revealed that the protective association of GDMT against major bleeds remained statistically significant after excluding patients receiving DAPT with both in loading dose, excluding patients died within 48 hours of admission, excluding patients with Killip Class IV, excluding patients receiving unfractionated heparin, and excluding patients with previous history of hemorrhagic stroke. Additional sensitivity analyses based on a 1-to-3 matched cohort (covariate balance after matching was shown in **Supplemental Table 3** and **Supplemental Fig. 1**, and the results in detail was shown in **Supplemental Fig. 2**), revealed that GDMT-associated reduction in major bleeds was consistent for composite bleeds, as well as for BARC-, TIMI-, and PLATO-defined major bleeds. Moreover, GDMT was associated with similar magnitude of reductions in ischemic events (OR: 0.57, 95%CI: 0.43–0.75) and in-hospital mortality (OR: 0.39, 95%CI: 0.28–0.56) as observed in the 1-to-2 matched cohort. The results based on inverse probability weighting algorithm also confirmed the above findings (**Supplemental Fig. 3**).

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 hours, was associated with a 28% reduction in major bleeding risk among STEMI patients treated with PCI. This finding was consistent by 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, among patients treated with PCI and without a missing value for time delay for PCI, 0.5% (1824/36362, shown in Fig. 1) had a clear contra-indication to GDMT, whereas only 35.5% (12,262/34,538) patients without a clear contra-induction received GDMT within the first 24 hours. 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.

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,[18] which would more likely to occur during hospitalization following PCI,[19] and independently predicted mortality after STEMI.[20] Current

measures to reduce bleeding risk in this clinical scenario are still 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 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 GDMT and bleeding risk STEMI during hospitalization. Bleeding complications after PCI is generally categorized as procedure-related bleeding which usually occurs within 7 days and during hospitalization, and non-procedure related bleeding, also called spontaneous bleedings that occurs from 7 days after discharge.[21] In this regard, our findings provide the first evidence that early GDMT was associated with reduced risk for procedure-related bleeding in STEMI patients.

Notably, recent evidence also supports a protective association between GDMT and non-procedure related bleeding following PCI. A post-hoc analysis of DAPT (Dual Antiplatelet Therapy) 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.[22] The patients included in the DAPT study were free of major adverse cardiovascular or cerebrovascular event, repeat revascularization or GUSTO (Global Use of Strategies to Open Occluded Arteries) moderate or severe bleeding at 12 months. During an additional 18 months of $P2Y_{12}$ 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%, 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 hours was only 35.5%. This percentage is significantly lower than reported by PROMETHEUS Registry (69.4%).[23] Given the clinical benefits of early GDMT presented in the present study, specific efforts should be made in the future to address the underuse of GDMT in clinical practice in China.

Due to the proved clinical efficacy in the secondary prevention of ASCVD, GDMT is currently recognized as the background treatment for STEMI patients. Therefore, it is difficult to establish a causal relationship between GDMT and its bleeding avoidance potential in randomized controlled trial. Currently, scatter evidence existed supporting the bleeding reduction potential for individual component of GDMT. 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.[24, 25] 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 regards to β-blocker, 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-blocker have been recommended for primary and secondary prevention of gastrointestinal bleeding in patients with cirrhosis

and esophageal varices.[9] Collectively, the available evidence of main components of GDMT, provides pharmacological proof that early GDMT 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 GDMT 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 which 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,[26] our findings should not be overgeneralized. Future studies from other populations are warranted to confirm our findings.

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 GDMT, i.e., the combined use of β-blocker, ACEI/ARB and statin within the first 24 hours, 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 use of GDMT in this patient population.

Declarations

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Contributors

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 table and figure generation. YH, JL and DZ supervised the CCC-ACS project, and interpreted the data. All authors read and approved the final manuscript.

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Data Availability

The data, analytic methods, and study materials will be made available for onsite audit by third parties for purposes of reproducing the results or replicating the procedure.

Disclosures

None.

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Figures

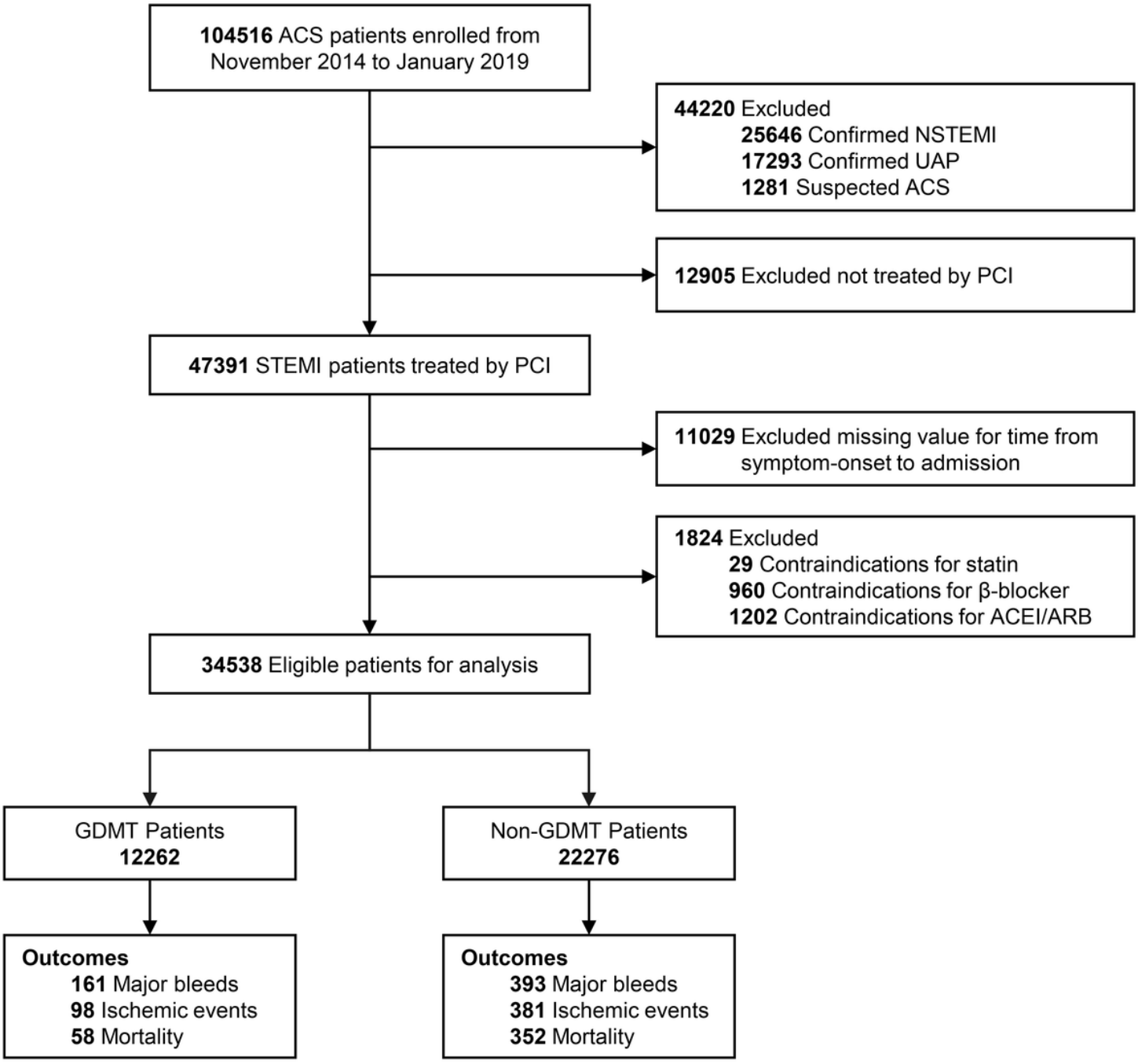

Figure 1

A schematic overview illustrating participant enrollment and the exclusion and inclusion criteria Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; GDMT, guideline-directed medical therapy; NSTEMI, Non-ST-elevation Myocardial Infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation Myocardial Infarction; UAP, unstable angina pectoris.

Figure 2

A Love-Plot illustrating the effect of matching were evaluated by comparing the absolute standardized difference 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; HDL-C, high density lipoprotein cholesterol; HR, heart rate; LDL-C, low density lipoprotein cholesterol; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TG, triglycerides.

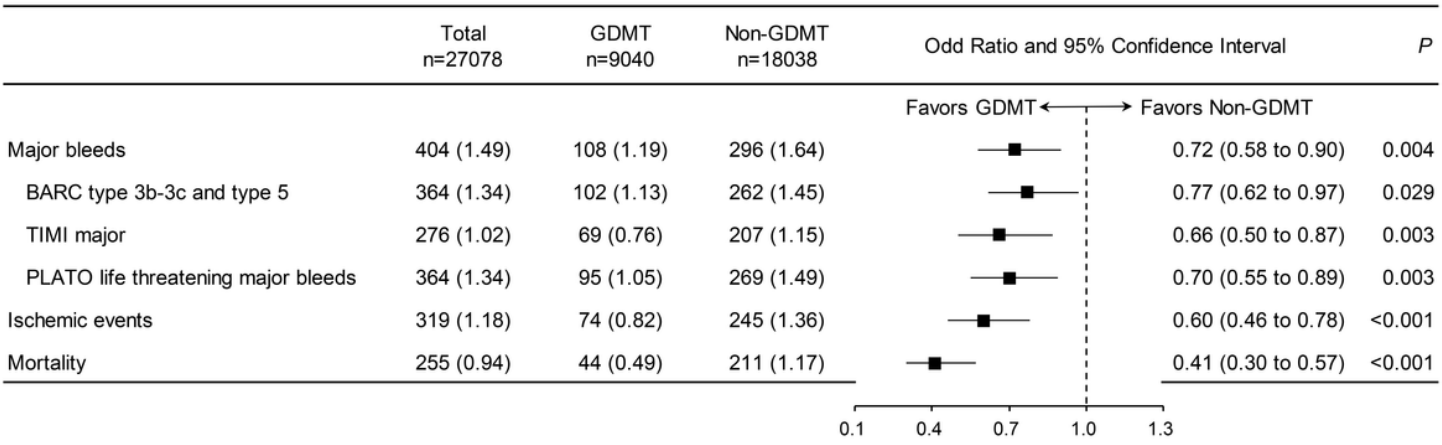

Figure 3

The association between GDMT status and risk of in-hospital major bleeding, ischemia and mortality. Abbreviations: BARC, Bleeding Academic Research Consortium; GDMT, guideline-directed medical therapy; PLATO, PLATelet inhibition and patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction.

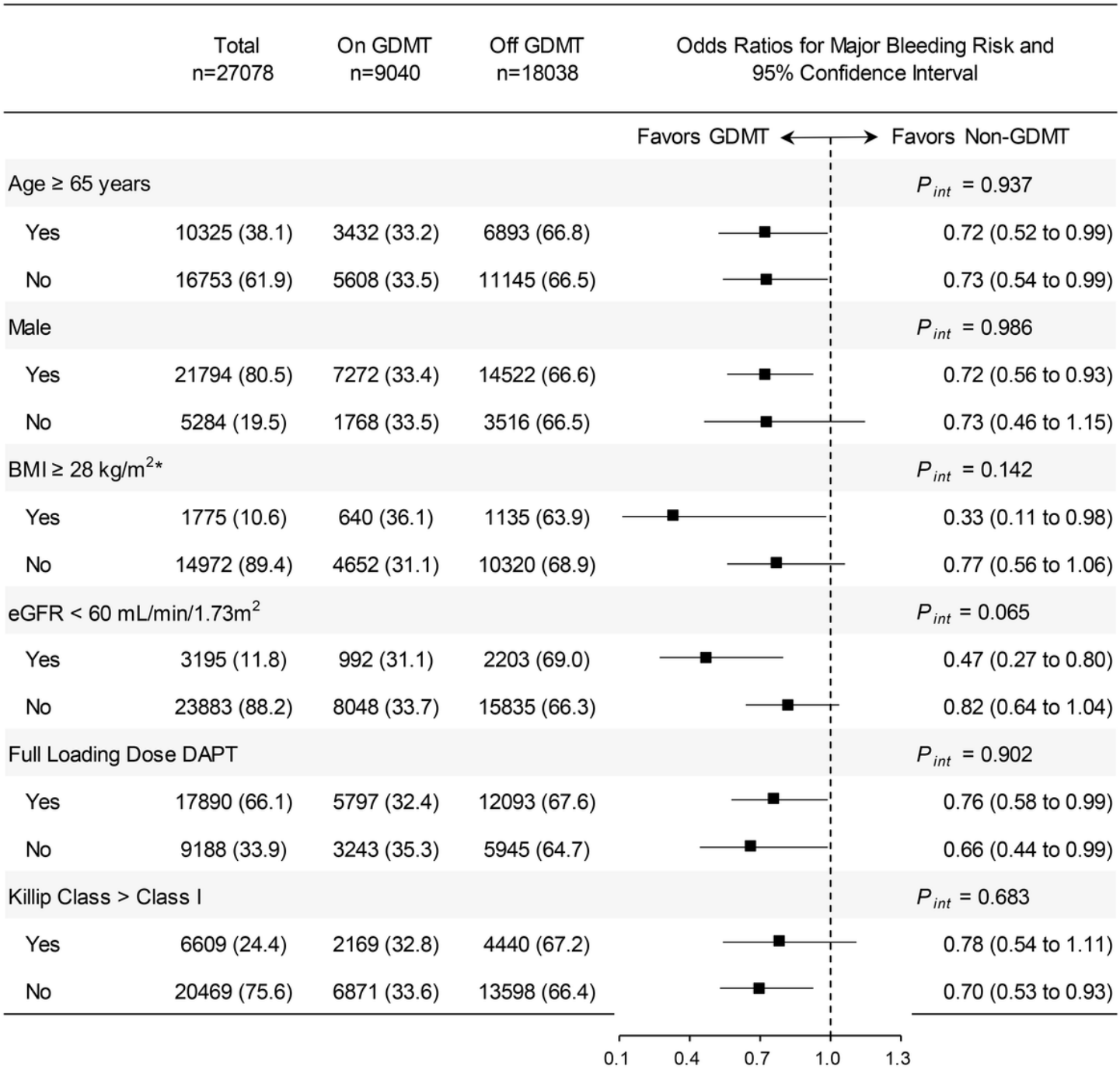

Figure 4

Subgroup analysis. * BMI was derived from 16,747 participants without missing value. Abbreviations: BMI, Body Mass Index; DAPT, dual anti-platelet therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy.

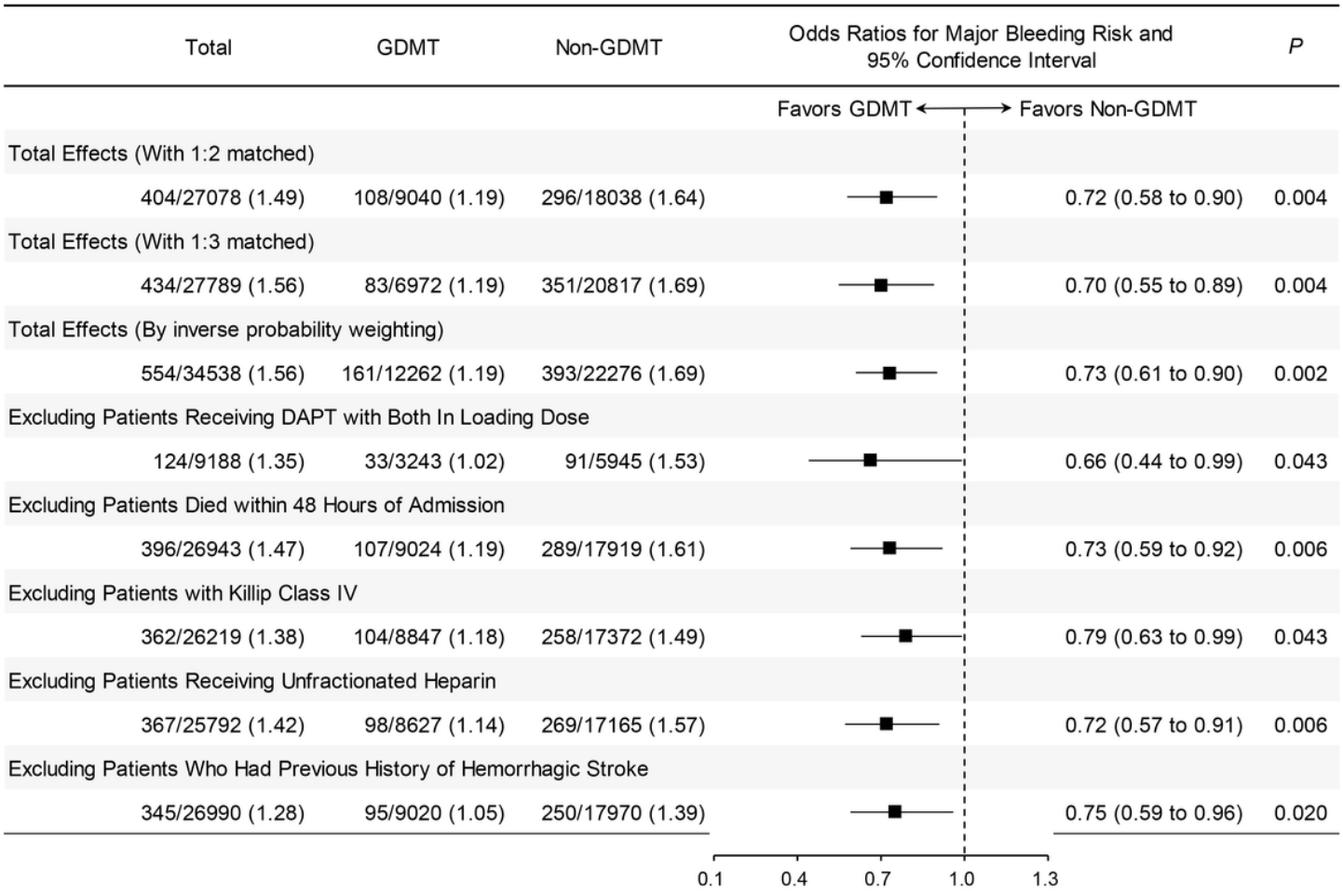

Figure 5

Sensitivity analysis. Abbreviations: DAPT, dual anti-platelet therapy; GDMT, guideline-directed medical therapy.

Supplementary Files

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