Association Between Platelet Glycoprotein IIb/IIIa Inhibition and In-Hospital Outcomes in ST-Elevation Myocardial Infarction Patients Treated with Coronary Thrombus Aspiration: Findings from the CCC-ACS Project

Wennan Liu
Tianjin Medical University General Hospital
Ziping Li
Tianjin Medical University General Hospital
Tianqi Yang
Tianjin Medical University General Hospital
Geru A
Tianjin Medical University General Hospital
Haonan Sun
Tianjin Medical University General Hospital
Hangkuan Liu
Tianjin Medical University General Hospital
Xiwen Song
Tianjin Medical University General Hospital
Zhengyang Jin
Tianjin Medical University General Hospital
Linjie Li
Tianjin Medical University General Hospital
Yongle Li
Tianjin Medical University General Hospital
Yongchen Hao
Capital Medical University Affiliated Anzhen Hospital
Jing Liu
Capital Medical University Affiliated Anzhen Hospital
Dong Zhao
Capital Medical University Affiliated Anzhen Hospital
Xin Zhou
Tianjin Medical University General Hospital

Qing Yang

cardio-yq@tmu.edu.cn

Tianjin Medical University General Hospital https://orcid.org/0000-0001-5481-9079

Research Article

Keywords: Platelet Glycoprotein IIb/IIIa Inhibitors, ST-elevation myocardial infarction, Percutaneous coronary intervention, Bleeding

Posted Date: August 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1949081/v1

Version of Record: A version of this preprint was published at Cardiovascular Drugs and Therapy on November 7th, 2022. See the published version at https://doi.org/10.1007/s10557-022-07398-w.

Abstract

Purpose: Thrombus aspiration in ST-elevation myocardial infarction (STEMI) with high thrombus burden did not improve clinical outcomes. The clinical efficacy of bailout use of platelet glycoprotein IIb/IIIa inhibitors (GPIs) in this clinical scenario remains unknown.

Methods: We assessed associations between GPI use and in-hospital major bleeds, ischemic events, and mortality among STEMI patients treated with percutaneous coronary intervention (PCI) and thrombus aspiration in a nationwide acute coronary syndrome registry (the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome project).

Results: A total of 5,896 STEMI patients who received thrombus aspiration were identified, among which 56.3% received GPI therapy. In a 1-to-1 propensity-score-matched cohort, compared with STEMI patients not treated with GPI, GPI use was associated with a 69% increase in major in-hospital bleeds, with an odds ratio (OR) of 1.69, a 95% confidence interval (CI) of 1.08 to 2.65, and a nonsignificant reduction in ischemic events (OR: 0.61, 95% CI: 0.36 to 1.06), as well as a neutral effect on mortality (OR: 0.93, 95% CI: 0.55 to 1.58). However, among patients aged < 65 years, GPI use was associated with a reduction in ischemic events (OR: 0.26, 95% CI: 0.08 to 0.77), and no significant increase in major bleeds (OR: 1.23, 95% CI: 0.67 to 2.25) was observed.

Conclusion: In a nationwide registry, routine use of GPI following thrombus aspiration was not associated with reduced in-hospital ischemic events and mortality, but at the cost of increased major bleeding. However, for patients aged < 65 years, there may be a potential net benefit.

Introduction

Intracoronary thrombosis-induced acute vascular occlusion is the primary pathophysiological basis segment elevation myocardial infarction (STEMI).[1] Recent progress in reperfusion strategies, including primary percutaneous coronary intervention (PCI) and thrombolysis, as well as high-density antiplatelet and anticoagulation therapy, has greatly improved clinical outcomes in STEMI patients.[2, 3] However, high thrombus burden is still a clinical challenge in STEMI management and is associated with a greater risk of no- or slow-reflow phenomena, stent thrombosis, transmural necrosis, and death.[4] Although thrombus aspiration was designed to reduce distal embolization in patients with high thrombus burden, this approach has not been recommended as a routine procedure in high thrombus burden because of insufficient evidence of its clinical efficacy in recent meta-analysis,[5] although it may be considered in selective or bailout situations under recent clinical guidelines.[2, 3, 6-9]

Glycoprotein IIb/IIIa inhibitor (GPI) is a rapidly acting and potent antiplatelet agent. In recent years, with a new generation of drug-eluting stents and more potent oral $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor), GPI recommendations in STEMI guidelines have been scaled back from routine therapy to bailout use or selected-patients only in contemporary iterations.[2, 3] East Asians are at increased risk for

bleeding complications when treated with the standard dose of antithrombotic agents, a phenomenon known as the “East Asian Paradox.”[10] Notably, GPI is not recommended in Japan and is only considered in other East Asian countries and regions as a bailout strategy when there is evidence of large thrombus burden, slow- or no-reflow, and other thrombotic complications.[6-9] A previous meta-analysis based on an East Asian population suggested a possible synergistic effect between thrombus aspiration and GPI,[11] but this study was inconclusive because of the insufficient data and low quality of studies included. Nevertheless, a recent Korean registry study suggested that dual antiplatelet therapy (DAPT) plus a GPI regimen may increase the bleeding risk in acute myocardial infarction patients who present with intracoronary thrombus.[12] Thus, with potent platelet inhibition and wide use of the drug-eluting stent, evidence for the use of GPI in high thrombus burden STEMI patients who need thrombus aspiration remains elusive.

The Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) project is a collaborative effort of the American Heart Association and the Chinese Society of Cardiology aimed at improving the quality of care for acute coronary syndrome (ACS) patients in China.[13] Based on the CCC-ACS project, the current study evaluates the association between GPI use and in-hospital outcomes of STEMI patients with high thrombus burden who were treated with thrombus aspiration during the indexed PCI.

Methods

Study Design and Population

Our analysis was based on the CCC-ACS project, which is a nationwide registry jointly initiated by the American Heart Association and the Chinese Society of Cardiology from 2014. 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).

A total of 104,516 ACS patients were enrolled in the CCC-ACS project from November 2014 to July 2019. As shown in **Figure 1**, we included 5,896 patients (3,322 GPI users and 2,574 non-GPI users) for analysis after excluding the following groups: those admitted with a diagnosis of non-ST-elevation myocardial infarction; those who were not treated with PCI; those with a missing value for body weight; those who were not treated by thrombus aspiration therapy; and those who received GPI after the occurrence of an ischemic event during hospitalization. GPIs used in the CCC-ACS project included tirofiban, eptifibatide, abciximab, or others at any time during the indexed hospitalization.

Study Covariates

The following variables were treated as covariates for multivariable adjustment and propensity score matching: demographics (age, sex, and body weight); previous history (diabetes, hypertension,

dyslipidemia, smoking, MI, PCI, coronary artery bypass grafting, atrial fibrillation, heart failure, renal failure, ischemic stroke, hemorrhagic stroke, peripheral vascular disease, chronic obstructive pulmonary disease); on-admission clinical features [Killip class, peak levels of creatine kinase-MB (CK-MB) isoform, 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 (prehospital thrombolysis, aspirin, $P2Y_{12}$ inhibitors, statins, β-blockers, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), aldosterone antagonists and oral anticoagulants); in-hospital medications [DAPT status, $P2Y_{12}$ inhibitors (clopidogrel or ticagrelor), statins, β-blockers, ACEIs/ARBs, aldosterone antagonists, oral anticoagulants, and perioperative anticoagulants (unfractionated heparin, low molecular weight heparin (LMWH) and others)]; and PCI-related characteristics [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]. Estimated glomerular filtration rate (eGFR) was calculated according to the equation by chronic kidney disease.[14] DAPT status within the first 24 hours was defined by one of the following three categories: non-loading DAPT (DAPT not in loading dose), single-loading DAPT, and both-loading DAPT (DAPT both in loading dose). The loading dose of aspirin was defined as ≥ 150 mg. The loading dose of the $P2Y_{12}$ receptor inhibitor was defined as ≥ 300 mg for clopidogrel and ≥ 180 mg for ticagrelor. The definitions of the abovementioned study variables are listed in **Supplemental Table 1**.

Study Outcomes

The primary study outcome concerned major in-hospital bleeds, defined by any of the following three major bleeding definitions that occurred during hospitalization: (a) Bleeding Academic Research Consortium (BARC) type 3b (defined as a hemoglobin drop of ≥ 5 g/dL or cardiac tamponade or bleeding requiring surgical intervention or bleeding requiring intravenous vasoactive agents), 3c (intracranial hemorrhage) and type 5 (fatal bleeding); (b) Thrombolysis in Myocardial Infarction (TIMI) major bleeding (defined as intracranial hemorrhage or clinically overt bleeding associated with a hemoglobin drop of ≥ 5 g/dL, or fatal bleeding); and (c) PLATelet inhibition and patient Outcomes (PLATO) life-threatening bleeding (defined as fatal bleeding, intracranial bleeding, intraoperative bleeding with cardiac tamponade, severe hypotension, hypovolemic shock because of 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). Coronary artery bypass-grafting-related bleeding was excluded. Other study outcomes included in-hospital mortality and less severe but clinically significant in-hospital bleeds (defined as a hemoglobin drop of 3 to 5 g/dL). The associations between GPI use and ischemic events and all-cause in-hospital mortality were also examined. We defined ischemic events as the occurrence of reinfarction, ischemic stroke, non-bleeding related fatal events, and in-stent thrombosis. The data of study outcomes above for this study were collected from their medical records.

Statistical Analysis

Results obtained from continuous data with normal distribution are presented as means and standard deviations. Those from non-normal continuous data are presented as medians with 25^{th} and 75^{th} percentiles, and those from categorical data are presented as numbers and percentages. The absolute standardized difference (ASD), which is superior to rank-sum tests or t-tests because it is independent of sample size, was used for between-group comparisons. The between-group imbalances were considered ideal if the ASD was less than 10% (Stata command “stddiff”). We used propensity score matching to balance the differences in patient demographics, medical history, and pre-admission and in-hospital management strategies between GPI users and non-GPI users. We developed a non-parsimonious multivariable logistic regression model to estimate a propensity score for GPI status (yes or no) as the dependent variable. Then, a propensity score matching of a maximal ratio of 1-to-1, 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 and ≥ 65 years), sex, eGFR, Killip class (Class I vs. > Class I), DAPT status (full loading or not), and Low Molecular Weight Heparin LWMH (use or not).

Finally, we performed the following sensitivity analyses based on the matching cohort that excluded the following: (a) patients who died within 48 hours of admission; (b) patients with Killip Class IV; (c) patients receiving ticagrelor; (d) patients receiving DAPT with both in loading dose; (e) femoral PCI; and (f) patients receiving unfractionated heparin (nonoperative, unfractionated heparin use). Additionally, an inverse probability weighting based on multivariate logistic regression (Stata command “teffects ipw”) was used as a sensitivity analysis to validate the primary findings.

We imputed data for variables with missing values using the sequential regression multiple imputation method by IVEware (version 0.2; Survey Research Center, University of Michigan, Ann Arbor, MI), as previously described.[15] The missing rates of the study variables are shown in **Supplemental Table 2.** 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

Among 3,322 GPI users and 2,574 non-GPI users, as shown in **Supplemental Table 3**, GPI users were younger, more likely to be male and dyslipidemia patients, with higher levels of body weight and hemoglobin, and less likely to receive prehospital thrombolysis and prehospital medications (aspirin, $P2Y_{12}$ inhibitors, statins, β-blocker, and aldosterone antagonist). After propensity score matching, a cohort comprising 2,219 GPI users (66.7% of the total GPI population) and 2,219 non-GPI users was constructed, with well-balanced clinical characteristics in terms of demographics, pre-admission

characteristics, medical history, admission characteristics, and in-hospital management strategies. The baseline characteristics of the post-matching cohort are shown in **Table 1**, and the ASD between pre- and post-matched cohorts is shown in **Figure 2**.

Associations Among GPI, Major In-Hospital Bleeds, Ischemic Events, and Mortality

In the propensity-score-matched cohort, a total of 83 composite major bleeds, 55 ischemic events, and 56 deaths were recorded, with incidence rates of 1.90%, 1.20%, and 1.30%, respectively. Compared with non-GPI users, GPI use was associated with a 69% increase in major bleeds, with an odds ratio (OR) of 1.69, a 95% confidence interval (CI) of 1.08 to 2.65, and a nonsignificant reduction in ischemic events (OR: 0.61, 95% CI: 0.36 to 1.06), as well as a neutral effect on in-hospital mortality (OR: 0.93, 95% CI: 0.55 to 1.58). Notably, GPI-associated increase in bleeding risk was consistent for BARC- (OR: 1.63, 95% CI: 0.99 to 2.66), TIMI- (OR: 1.83, 95% CI: 1.09 to 3.09), and PLATO- (OR: 1.80, 95% CI: 1.13 to 2.88) defined major bleeds (**Figure 3**). By using inverse probability weighting, we also confirmed the abovementioned findings (**Supplemental Figure 1**). As shown in **Figure 4 and Supplemental Figure 2**, there was no significant interaction across subgroups, and GPI-associated bleeding risk was more pronounced in patients with advanced age (OR: 2.52, 95% CI: 1.27 to 5.00), in males (OR: 1.82, 95% CI: 1.11 to 2.97), and in patients receiving LMWH therapy (OR: 2.26, 95% CI: 1.22 to 4.17). Similarly, the association of GPI use with ischemic events (**Figure 4 and Supplemental Figure 3**) and mortality (**Figure 4 and Supplemental Figure 4**) across subgroups was generally in agreement with the main findings. Notably, as shown in **Figure 4**, a significant interaction between age subgroup and ischemic events was observed among patients aged < 65 years (OR: 0.26, 95% CI: 0.08 to 0.77) versus patients aged ≥ 65 years. Considering the nonsignificant increase in major bleeding risk in this subgroup (**Figure 4**), these results indicate a potential benefit of GPI use in STEMI patients aged < 65 years following thrombus aspiration.

Sensitivity Analysis

Figure 5 displays the sensitivity analyses for major in-hospital bleeding. GPI use-associated risk for major bleeds remained consistent in multiple sensitivity analyses. In terms of in-hospital ischemic events and mortality, additional sensitivity analyses revealed similar results that agreed with the main findings. (**Supplemental Figures 5 and 6**).

Discussion

In a nationwide registry of STEMI patients receiving contemporary management, we demonstrated that GPI use following thrombus aspiration was not associated with reduced in-hospital ischemia events and mortality, but at the cost of increased major bleeding. These findings were found to be consistent using multiple sensitivity analyses. However, our analysis also showed a possible beneficial GPI-use effect in STEMI patients aged < 65 years, in terms of a significant reduction in ischemic events and a nonsignificant increase in major bleeds. Therefore, the study's evidence does not support routine GPI use following thrombus aspiration, but STEMI patients aged < 65 years may benefit from this bailout strategy.

Most patients included in the study received the standard treatment recommended by the guidelines.[2, 3, 6-9] For example, about 97% of the patients received at least one loading dose of DAPT treatment, and about 84% received parenteral anticoagulant agents. Ticagrelor accounted for about 40% of $P2Y_{12}$ inhibitors, and clopidogrel accounted for about 60%; 92% of patients were administered transradial access for PCI, which had been proven to significantly reduce the risk of bleeding.

Sufficient clinical evidence shows that high thrombus burden still appears to be an important risk factor for STEMI patients. Large thrombus burden increases the risk of no- or slow-reflow and distal embolization,[4, 15] which may lead to more cardiovascular death, heart failure, or cardiogenic shock.[16] Distal embolization of micro-thrombi and plaque-material-induced obstruction of the microvasculature may be one important mechanism of poor prognosis,[17] and there is evidence that intrinsic platelet reactivity was higher with greater thrombus burden, which predicts the thrombus burden may be a risk marker of system ischemic risk as well as a therapeutic target.[18] In view of these mechanisms, the potential effective schemes considered in the current treatment of high thrombus burden may be thrombus aspiration alone or with GPI. In support of these pathological mechanisms, a recent randomized controlled trial showed that even under the current intensive treatment measures (60.8% ticagrelor and 50.7% thrombus aspiration), GPI use in STEMI patients with high thrombus burden is capable of improving myocardial perfusion, as shown by lower TIMI frame counts.[19] However, this study was underpowered to detect differences in bleeding and mortality risk.

Thrombus aspiration can be used to evacuate coronary thrombus prior to stent deployment, so it may improve the blood flow of coronary microcirculation and reduce the risk of no-reflow.[20] However, even in patients with high thrombotic load, it was demonstrated that routine thrombus aspiration does not improve outcomes.[16] Limitations of the current manual thrombus aspiration technique probably include downstream thromboembolism, limited ability to deal with large organized thrombi, and embolization of thrombus to other vascular territories during removal of the aspiration catheter.[5] GPI was considered to have a synergistic effect with thrombus aspiration because it could further dissolve residual thrombus in the microvasculature after most thrombotic materials were retrieved by thrombus aspiration.[21]

The advantage of GPIs is their rapid and powerful antiplatelet effect. Although there is no clinical evidence, GPI could be a bailout therapy in the event of a large thrombus and other thrombotic complications.[2, 3] However, our study, based on the Chinese population, found that in the era of wide use of new $P2Y_{12}$ and new-generation drug-eluting stents, routine GPI use in STEMI patients who received thrombus aspiration did not decrease in-hospital ischemic events, but significantly increased the risk of bleeding. These findings are consistent with other recent clinical studies on the application of GPI bailout use.[22, 23] However, an important finding in the present study was a statistically significant interaction between aging (≥ 65 years vs. < 65 years) and GPI-associated major bleeding risk: Patients aged ≥ 65 years had increased risk of major bleeding, while those aged < 65 years may benefit from GPI treatment, as shown by a reduction in ischemic events and a nonsignificant increase in major bleeding risk. Indeed, advanced age is generally regarded as a risk factor for bleeding risk among patients receiving

antithrombotic therapy. [24-26] Mechanistically, age-related physiological changes [27] (i.e., the increasing levels of fibrinogen, factor [F] VII, FVIII, plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor) made the formation of thrombus in the elderly more intricate, which may limit the efficacy of platelet glycoprotein IIb/IIIa inhibition. However, decline of liver or kidney function and age-related amyloid angiopathy may heighten the risk of bleeding. Therefore, advanced age seems to be a key factor affecting the risk and benefit to GPI users.

To our knowledge, the present work is the largest sample size empirical study on the association between GPI use and in-hospital outcomes in STEMI patients treated with coronary thrombus aspiration. Although multiple statistical approaches have confirmed the key findings, several limitations should, nonetheless, be acknowledged. First, in an observational study, we cannot exclude the possible impact of unmeasured factors. For example, according to existing STEMI guidelines, thrombus aspiration is only suitable for patients with high thrombus burden, so this study assumes all patients undergoing thrombus aspiration have high thrombus burden, but it lacks any quantitative analysis of thrombus load. Second, the entire included population was Chinese. Because ethnic differences affect the risks of bleeding and ischemia, the conclusions of this study should be extended to other populations with caution.

In conclusion, in a nationwide ACS registry in China, the routine use of GPI did not reduce the incidence of in-hospital ischemic events in STEMI patients treated with thrombus aspiration, but significantly increased the risk of major bleeding. However, a reduced risk for ischemic events and nonsignificant increase in major bleeding risk was observed in patients aged < 65 years old, indicating the potential benefit of GPI use in this subgroup. These findings need to be validated in other populations.

Declarations

Author Declarations

Funding

This work was supported by a collaborative program of the American Heart Association and the Chinese Society of Cardiology. The American Heart Association was funded by Pfizer and AstraZeneca for the quality improvement initiative through an independent grant for learning and change. This work was also supported by the National Key R&D Program of China (Nos. 2020YFC2004700, 2020YFC2004706), National Natural Science Foundation of China (No. 81970304) and Tianjin Municipal Science and Technology Commission (No. 18ZXZNSY00290).

Conflicts of interest/Competing interests

The authors declare that there are no conflicts of interest or competing interests to report.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Authors' contributions

The article was written on behalf of the CCC-ACS project investigators. XZ, QY and YL conceived and designed the study, supervised the analysis process, interpreted the data and revised the manuscript. WL and ZL analyzed the data and drafted the manuscript. WL, ZL, TY, 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.

Ethics approval

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

Consent to participate

Not applicable.

Consent for publication

Not applicable.

References

1. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J. 2013;34:719–28. doi:10.1093/eurheartj/ehs411.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–77. doi:10.1093/eurheartj/ehx393.
3. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol. 2016;67:1235–50. doi:10.1016/j.jacc.2015.10.005.
4. Montalto C, Kotronias RA, Marin F, Terentes-Printzios D, Shanmuganathan M, Emfietzoglou M, Scalamera R, Porto I, Langrish J, Lucking A, et al. Pre-procedural ATI score (age-thrombus burden-index of microcirculatory resistance) predicts long-term clinical outcomes in patients with ST

elevation myocardial infarction treated with primary percutaneous coronary intervention. Int J Cardiol. 2021;339:1–6. doi:10.1016/j.ijcard.2021.07.040.

5. Jolly SS, James S, Džavík V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, et al. Thrombus Aspiration in ST-Segment-Elevation Myocardial Infarction: An Individual Patient Meta-Analysis: Thrombectomy Trialists Collaboration. Circulation. 2017;135:143–52. doi:10.1161/circulationaha.116.025371.
6. [2019 Chinese. Society of Cardiology (CSC) guidelines for the diagnosis and management of patients with ST-segment elevation myocardial infarction]. Zhonghua xin xue guan bing za zhi. 2019;47:766–83. doi:10.3760/cma.j.issn.0253-3758.2019.10.003.
7. Chang K, Ahn Y, Lim S, Yang JH, Lee KY, Choo EH, Kim HK, Nam CW, Kim W, Hwang JY, et al. 2021 Korean Society of Myocardial Infarction Expert Consensus Document on Revascularization for Acute Myocardial Infarction. Korean Circ J. 2021;51:289–307. doi:10.4070/kcj.2021.0043.
8. Li YH, Lee CH, Huang WC, Wang YC, Su CH, Sung PH, Chien SC, Hwang JJ. 2020 Focused Update of the 2012 Guidelines of the Taiwan Society of Cardiology for the Management of ST-Segment Elevation Myocardial Infarction. *Acta Cardiol Sin*. 2020;36:285–307. doi: 10.6515/acs.202007_36(4).20200619a.
9. Kimura K, Kimura T, Ishihara M, Nakagawa Y, Nakao K, Miyauchi K, Sakamoto T, Tsujita K, Hagiwara N, Miyazaki S, et al. JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome. Circ J. 2019;83:1085–196. doi:10.1253/circj.CJ-19-0133.
10. Kim HK, Tantry US, Smith SC Jr, Jeong MH, Park SJ, Kim MH, Lim DS, Shin ES, Park DW, Huo Y, et al. The East Asian Paradox: An Updated Position Statement on the Challenges to the Current Antithrombotic Strategy in Patients with Cardiovascular Disease. Thromb Haemost. 2021;121:422–32. doi:10.1055/s-0040-1718729.
11. Wu JH, Hao PP, Chen YG, Li RJ. Intracoronary Glycoprotein IIb/IIIa Inhibitors Improve Short-Term Mortality and Reinfarction in East Asian Patients with ST-Segment Elevation Myocardial Infarction after Thrombus Aspiration: A Meta-Analysis. Evid Based Complement Alternat Med. 2018;2018:5174714. doi:10.1155/2018/5174714.
12. Zheng C, Kang J, Yang HM, Han JK, Park KW, Kang HJ, Koo BK, Kim HS. Safety and Efficacy of Glycoprotein IIb/IIIa Inhibitors in Patients With Acute Myocardial Infarction in the Presence of Intracoronary Thrombus: An Analysis From the Grand Drug-eluting Stent Registry. Clin Ther. 2020;42:954–8.e956. doi:10.1016/j.clinthera.2020.02.022.
13. Hao Y, Liu J, Liu J, Smith SC Jr, Huo Y, Fonarow GC, Ma C, Ge J, Taubert KA, Morgan L, et al. Rationale and design of the Improving Care for Cardiovascular Disease in China (CCC) project: A national effort to prompt quality enhancement for acute coronary syndrome. Am Heart J. 2016;179:107–15. doi:10.1016/j.ahj.2016.06.005.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12. doi:10.7326/0003-4819-150-9-200905050-00006.

15. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, Woldman S, Jain AK, Knight CJ, Baumbach A, et al. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. 2020;76:1168–76. doi:10.1016/j.jacc.2020.07.022.
16. Jolly SS, Cairns JA, Lavi S, Cantor WJ, Bernat I, Cheema AN, Moreno R, Kedev S, Stankovic G, Rao SV, et al. Thrombus Aspiration in Patients With High Thrombus Burden in the TOTAL Trial. J Am Coll Cardiol. 2018;72:1589–96. doi:10.1016/j.jacc.2018.07.047.
17. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J. 2014;35:1101–11. doi:10.1093/eurheartj/eht513.
18. Alexopoulos D, Xanthopoulou I, Tsigkas G, Damelou A, Theodoropoulos KC, Makris G, Gizas V, Kassimis G, Davlouros P, Hahalis G. Intrinsic platelet reactivity and thrombus burden in patients with ST-elevation myocardial infarction. Thromb Res. 2013;131:333–7. doi:10.1016/j.thromres.2013.02.010.
19. Huang D, Qian J, Liu Z, Xu Y, Zhao X, Qiao Z, Fang W, Jiang L, Hu W, Shen C, et al. Effects of Intracoronary Pro-urokinase or Tirofiban on Coronary Flow During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: A Multi-Center, Placebo-Controlled, Single-Blind, Randomized Clinical Trial. Front Cardiovasc Med. 2021;8:710994. doi:10.3389/fcvm.2021.710994.
20. Mahmoud KD, Zijlstra F. Thrombus aspiration in acute myocardial infarction. Nat Rev Cardiol. 2016;13:418–28. doi:10.1038/nrcardio.2016.38.
21. Zhou SS, Tian F, Chen YD, Wang J, Sun ZJ, Guo J, Jin QH. Combination therapy reduces the incidence of no-reflow after primary per-cutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction. J Geriatr Cardiol. 2015;12:135–42. doi:10.11909/j.issn.1671-5411.2015.02.003.
22. Abtan J, Ducrocq G, Steg PG, Stone GW, Mahaffey KW, Gibson CM, Hamm C, Price MJ, Prats J, Elkin S, et al. Characteristics and outcomes of patients requiring bailout use of glycoprotein IIb/IIIa inhibitors for thrombotic complications of percutaneous coronary intervention: An analysis from the CHAMPION PHOENIX trial. Int J Cardiol. 2019;278:217–22. doi:10.1016/j.ijcard.2018.11.114.
23. Velibey Y, Guvenc TS, Demir K, Oz A, Akdeniz E, Guvenc RC, Guzelburc O, Yildiz U, Safak A, Kalenderoglu K, et al. Effects of Bailout Tirofiban on In-Hospital Outcomes and Long-Term Mortality in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention. Angiology. 2019;70:431–9. doi:10.1177/0003319718808911.
24. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet. 2017;390:490–9. doi:10.1016/s0140-6736(17)30770-5.
25. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55:2556–66. doi:10.1016/j.jacc.2009.09.076.

26. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, Cannon CP, Rumsfeld JS, Roe MT, Alexander KP. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTG™. Am J Cardiol. 2011;107:1136–43. doi:10.1016/j.amjcard.2010.12.009.
27. Andreotti F, Rocca B, Husted S, Ajjan RA, Ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KA, Halvorsen S, et al. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2015;36:3238–49. doi:10.1093/eurheartj/ehv304.

Table

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

Characteristics	No. of Patients n=4438	GPI n=2219	Non-GPI n=2219	ASD, %
Demographics				
Age, year	59.8±12.7	59.7±12.4	60.0±12.9	2.69
Male, n (%)	3669(82.7)	1837(82.8)	1832 (82.6)	0.60
Weight, kg	70.0 (64.0-76.0)	70.0 (63.0-76.0)	70.0 (64.0-76.0)	0.42
Medical history				
Smoking, n (%)	2450 (55.2)	1222 (55.1)	1228 (55.3)	0.54
Hypertension, n (%)	2055 (46.3)	1019 (45.9)	1036 (46.7)	1.54
Diabetes, n (%)	841 (18.9)	417 (18.8)	424 (19.1)	0.81
Dyslipidemia, n (%)	297 (6.70)	150 (6.80)	147 (6.60)	0.54
MI, n (%)	229 (5.20)	118 (5.30)	111 (5.00)	1.43
PCI, n (%)	230 (5.20)	116 (5.20)	114 (5.10)	0.41
CABG, n (%)	7 (0.20)	4 (0.20)	3 (0.10)	1.14
COPD, n (%)	51 (1.10)	24 (1.10)	27 (1.20)	1.27
Heart failure, n (%)	11 (0.20)	6 (0.30)	5 (0.20)	0.91
Renal failure, n (%)	36 (0.80)	19 (0.90)	17 (0.80)	1.01
Atrial fibrillation, n (%)	71 (1.60)	35 (1.60)	36 (1.60)	0.36
Ischemic stroke, n (%)	285 (6.40)	148 (6.70)	137 (6.20)	2.02
Hemorrhagic stroke, n (%)	23 (0.50)	10 (0.50)	13 (0.60)	1.88
Peripheral vascular disease, n (%)	28 (0.60)	15 (0.70)	13 (0.60)	1.14
Clinical variables				
SBP, mmHg	125.2±22.7	124.9±23.2	125.5±22.2	2.79
DBP, mmHg	77.2±14.9	77.1±15.3	77.3±14.5	1.31
Heart rate, bpm	77.3±16.0	77.4±15.8	77.3±16.1	0.79
Killip Class >I, No. (%)	1080 (24.3%)	523 (23.6%)	557 (25.1%)	3.57
CK-MB peak, μg/L	48.9 (16.8-120)	48.8 (17.8-120)	49.0 (15.6-119.7)	0.71

LDL-C, mg/dL	107 (85.0-132)	107 (86.0-131)	106 (84.0-133)	0.41
HDL-C, mg/dL	40.0 (34.0-48.0)	41.0 (34.0-48.0)	40.0 (34.0-48.0)	1.01
TG, mg/dL	130 (89.0-190)	130 (90.0-188)	130 (89.0-194)	0.85
eGFR, mL/min/1.73m^2	87.2±22.8	87.3±22.3	87.0±23.3	1.29
Hemoglobin on admission, g/dL	142 (130-153)	142 (130-153)	141.4 (129-153)	0.16
Pre-hospital medications				
Pre-hospital thrombolysis, n (%)	47(1.10)	21 (0.90)	26 (1.20)	2.20
Aspirin, n (%)	655 (14.8)	326 (14.7)	329 (14.8)	0.38
P2Y$_{12}$ inhibitor, n (%)	523 (11.8)	264 (11.9)	259 (11.7)	0.70
Statin, n (%)	478 (10.8)	230 (10.4)	248 (11.2)	2.62
Oral anticoagulants, n (%)	12 (0.30)	7 (0.30)	5 (0.20)	1.74
β-blocker, n (%)	229 (5.20)	110 (5.00)	119 (5.40)	1.83
ACEI/ARB, n (%)	303 (6.80)	155 (7.00)	148 (6.70)	1.25
Aldosterone antagonist, n (%)	32 (0.70)	16(0.70)	16(0.70)	<0.01
In-hospital medications				
DAPT status after admission, n (%)				2.69
DAPT was not in loading dose	105 (2.40)	70 (3.20)	35 (1.60)	
One of DAPT in loading dose	1279 (28.8)	589 (26.5)	690 (31.1)	
DAPT both in loading dose	3054 (68.8)	1560 (70.3)	1494 (67.3)	
P2Y$_{12}$ inhibitor, n (%)				
Ticagrelor	1820 (41.0)	915 (41.2)	905 (40.8)	0.92
Clopidogrel	2790 (62.9)	1392 (62.7)	1398 (63.0)	0.56
Anticoagulation therapy, n (%)				
Unfractionated	396 (8.90)	201 (9.1)	195 (8.80)	0.95

heparin				
LMWH	3120 (70.3)	1571 (70.8)	1549 (69.8)	2.17
Others	133 (3.00)	69 (3.10)	64 (2.90)	1.32
Oral anticoagulants, n (%)	25 (0.60)	14.0 (0.60)	11 (0.50)	1.81
Statin, n (%)	4189 (94.4)	2099 (94.6)	2090 (94.2)	1.76
β-blocker, n (%)	2147 (48.4)	1077 (48.5)	1070 (48.2)	0.63
ACEI/ARB, n (%)	1749 (39.4)	876 (39.5)	873 (39.3)	0.28
Aldosterone antagonist, n (%)	668 (15.1)	326 (14.7)	342 (15.4)	2.02
PCI related				
Radial route for PCI, n (%)	4058 (91.4)	2032 (91.6)	2026 (91.3)	0.97
PCI type, n (%)				2.76
Primary, <12 h	3568 (80.4)	1782 (80.3)	1786 (80.5)	
Primary, ≥12 h	524 (11.8)	275 (12.4)	249 (11.2)	
Rescue	55 (1.20)	32 (1.40)	23 (1.00)	
Elective	291 (6.60)	130 (5.90)	161 (7.30)	

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; GPI, glycoprotein IIb/IIIa inhibitors; 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.

Figures

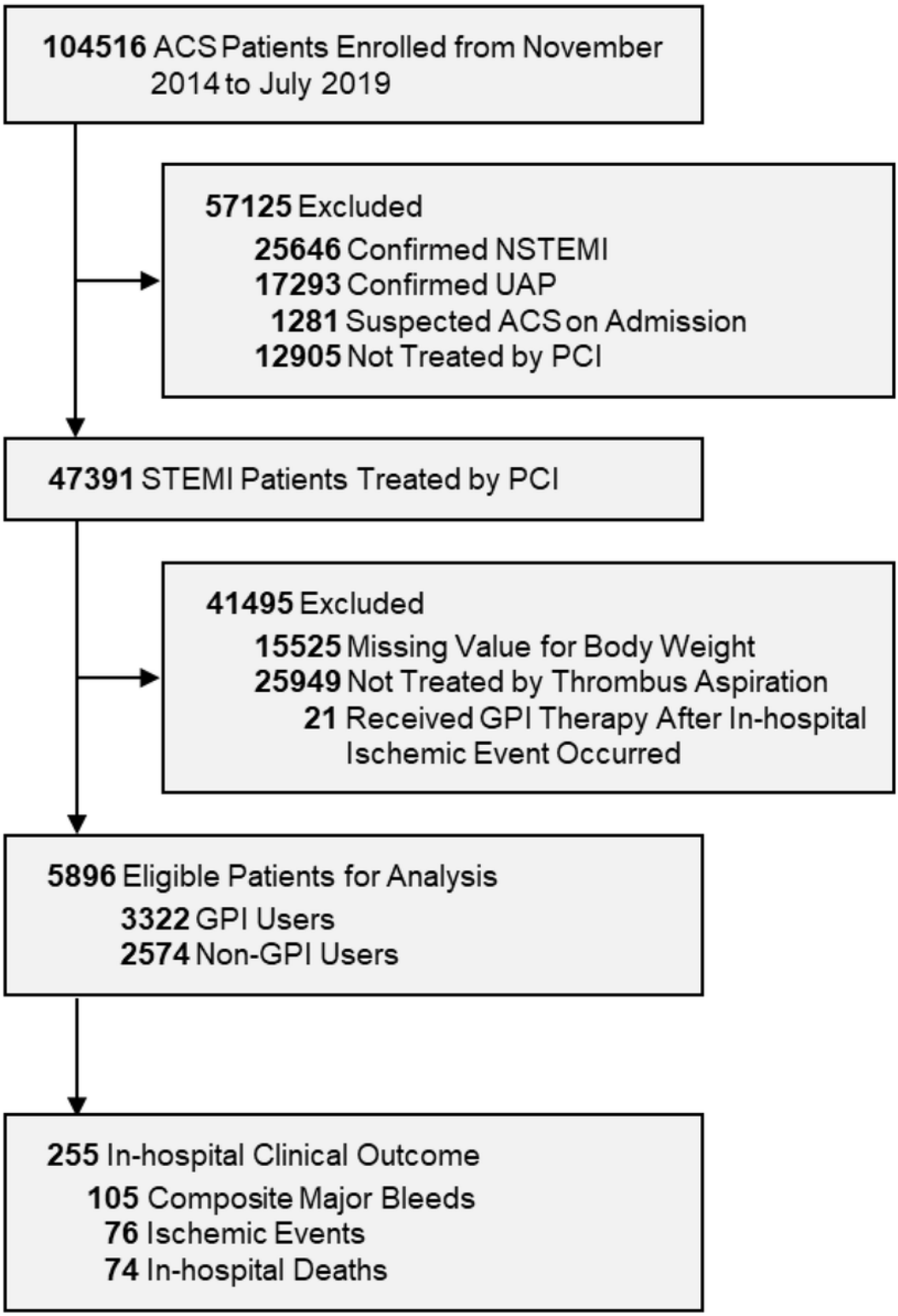

Figure 1

See image above for figure legend.

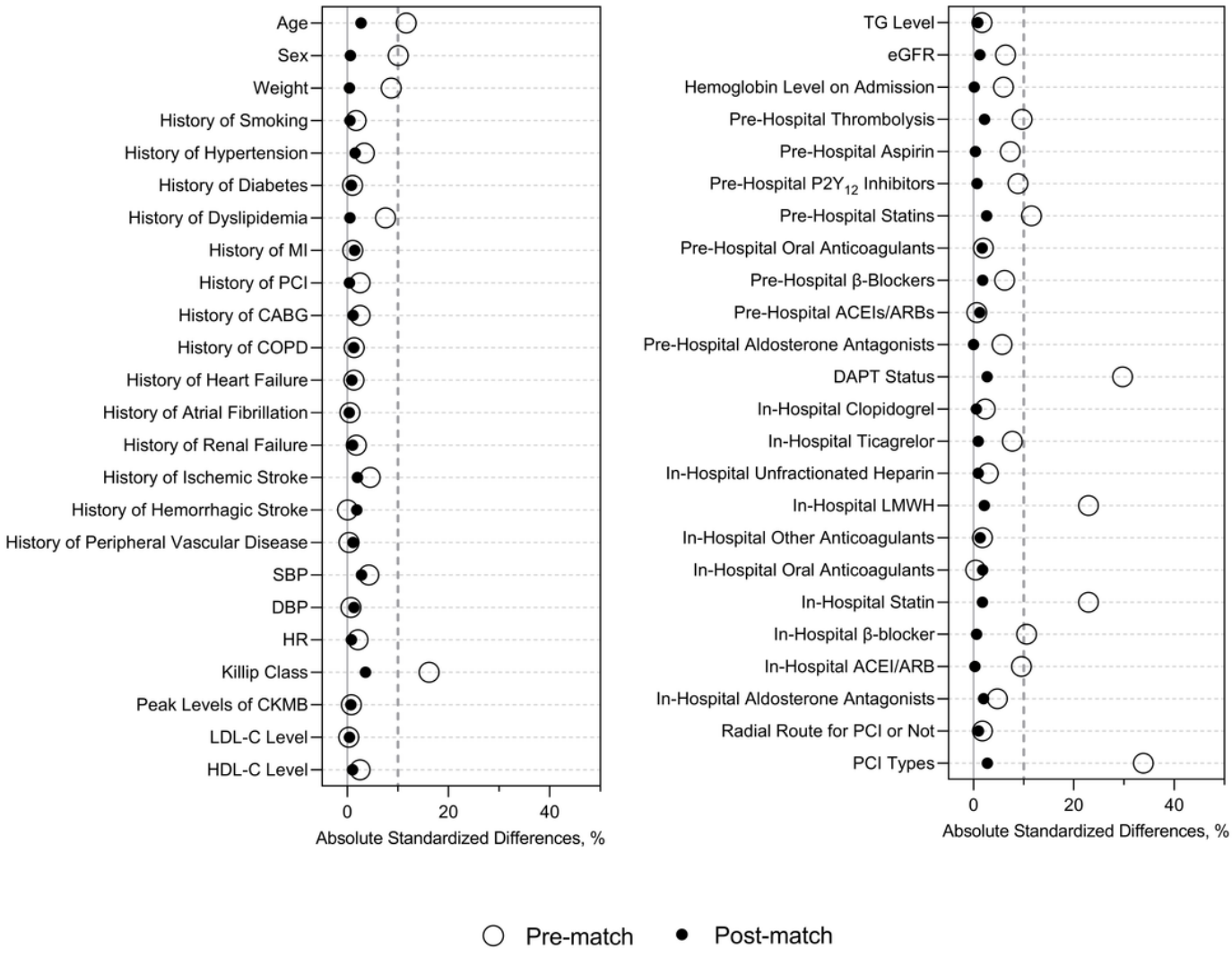

Figure 2

See image above for figure legend.

	Total n=4438	GPI n=2219	Non-GPI n=2219	Odd Ratio and 95% Confidence Interval	*P*
				Favors GPI ↔ Favors Non-GPI	
Major bleeds	83 (1.90)	52 (2.30)	31 (1.40)	1.69 (1.08 to 2.65)	0.020
BARC type 3b-3c and type 5	68 (1.50)	42 (1.90)	26 (1.20)	1.63 (0.99 to 2.66)	0.051
TIMI major	62 (1.40)	40 (1.80)	22 (1.00)	1.83 (1.09 to 3.09)	0.021
PLATO life threatening major bleeds	78 (1.80)	50 (2.30)	28 (1.30)	1.80 (1.13 to 2.88)	0.012
Ischemic events	55 (1.20)	21 (0.90)	34 (1.50)	0.61 (0.36 to 1.06)	0.078
Mortality	56 (1.30)	27 (1.20)	29 (1.30)	0.93 (0.55 to 1.58)	0.790

0.3 0.5 1.0 2.0 4.0

Figure 3

See image above for figure legend.

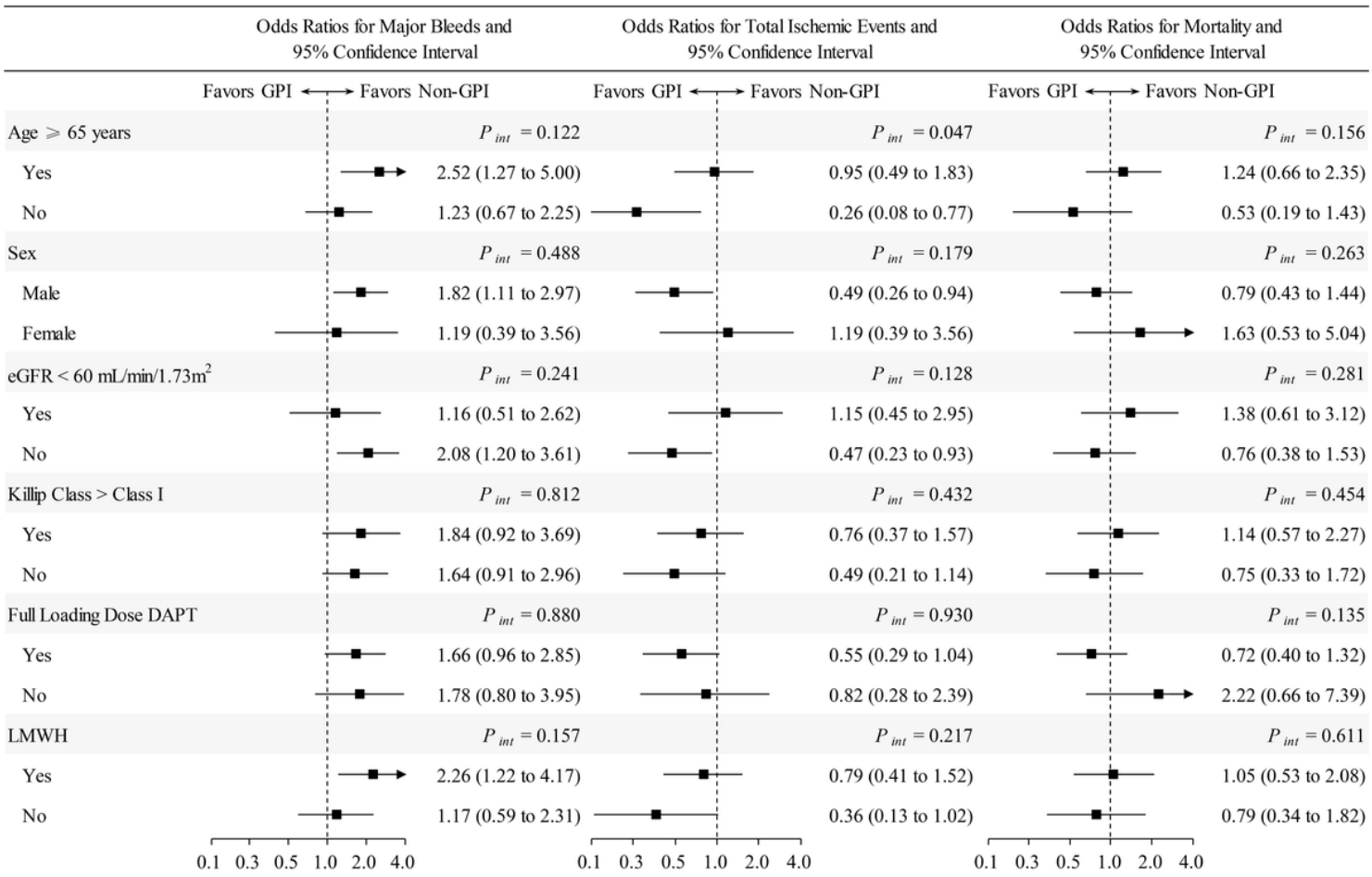

Figure 4

See image above for figure legend.

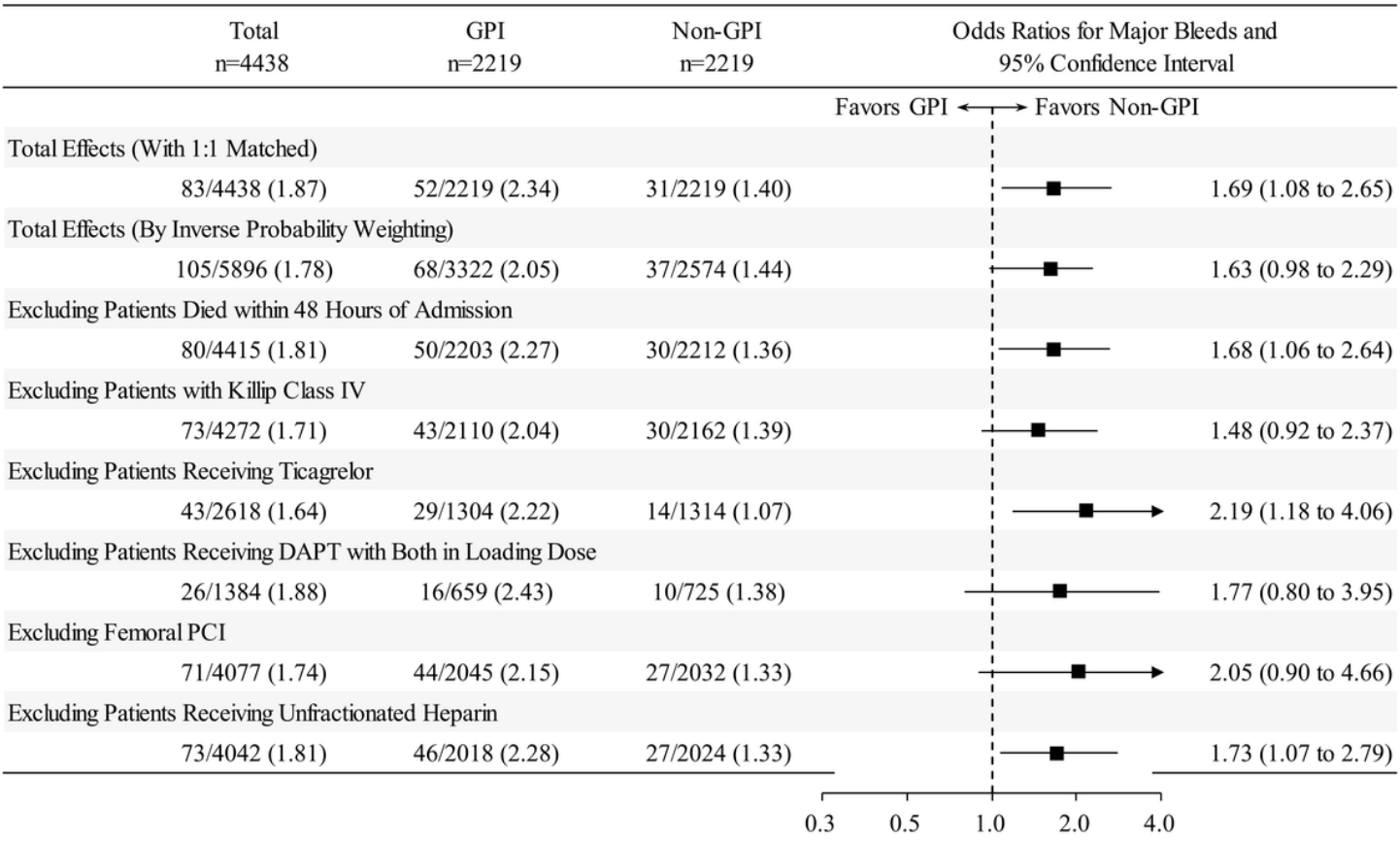

Figure 5

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalMaterial.docx