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► To cite this version:

Fabien Picard, Anastasia Sokoloff, Vincent Pham, Marine Diefenbronn, Driss Laghnam, et al.. Safety and benefit of Glycoprotein IIb/IIIa inhibitors in out of hospital cardiac arrest patients treated with percutaneous coronary intervention. *Resuscitation*, 2020, 157, pp.91 - 98. 10.1016/j.resuscitation.2020.10.030 . hal-03493290

HAL Id: hal-03493290

<https://hal.science/hal-03493290>

Submitted on 7 Nov 2022

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Safety and benefit of Glycoprotein IIb/IIIa inhibitors in out of hospital cardiac arrest patients treated with percutaneous coronary intervention.

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Running title: Glycoprotein IIb/IIIa inhibitors in OHCA patients

Funding: None

Relationship with industry: OV reports personal fees from Boston Scientific, Biotronik and Abbott Vascular. FP reports consulting and speaking fees from Biotronik and Sanofi. The other authors declare that they have no known conflicts of interest.

Wordcount: 3018

Abstract

Background: Out of hospital cardiac arrest (OHCA) patients requiring percutaneous coronary intervention (PCI) are at higher risk of both stent thrombosis and bleeding. The use of aggressive antiplatelet therapy could lead to a higher risk of bleeding in these patients. Indeed, data on glycoprotein IIb/IIIa inhibitor (GPI) use in this specific indication is scarce.

Aim: We sought to evaluate the benefit and safety of GPI use in OHCA patients requiring PCI.

Methods and Results: Between January 2007 and December 2017, we retrospectively included all consecutive patients treated with PCI for an OHCA from cardiac cause. Clinical, procedural data and in-hospital outcomes were collected. Three hundred and eighty-five patients were included. GPI were administrated in 41.3% of cases (159 patients). Patients who received GPI were younger, had less prior PCI, more often a TIMI 0 or 1 flow before PCI and thromboaspiration use. There were no differences regarding in-hospital definite stent thrombosis among the two groups (11.9% in the GPI group vs 7.1% in the non-GPI group, $p=0.10$) or in-hospital mortality (48.6% vs 49.3%, $p=0.68$). The incidence of any bleeding (33.3% vs. 19.6%; $p=0.002$), and major bleeding (BARC 3-5) (21.9% vs. 16.8%; $p=0.007$) was significantly higher in patients receiving GPI. Indeed, using multivariate analysis, GPI use was predictor of major bleeding (OR: 1.81; 95% CI: 1.06-3.08; $p=0.03$).

Conclusions: In patients treated with PCI for OHCA from cardiac cause, GPI use was associated with an increased risk of major bleeding events, without difference on in-hospital stent thrombosis or death.

Keywords: Cardiac-arrest, acute coronary syndrome, glycoprotein IIb/IIIa inhibitor, bleeding, stent thrombosis.

Wordcount: 244

60 **Abbreviations**

61 ACS: Acute coronary syndrome

62 PCI: Percutaneous coronary intervention

63 OHCA: Out-of-hospital cardiac arrest

64 STEMI: ST-elevation myocardial infarction

65 GPI: Glycoprotein IIb/IIIa inhibitors

66 ST: Stent thrombosis

67 ADP: Adenosine diphosphate

68 BMI: Body mass index

69 ORs: Odds-ratio

70 CI: Confidence interval

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Introduction

Acute coronary syndromes (ACS) are the leading cause of cardiac arrest [1]. European guidelines recommend urgent coronary angiography in a view for primary percutaneous coronary intervention (PCI) in survivors of out-of-hospital cardiac arrest (OHCA) [1-3]. A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI (Class I), and urgent angiography (and PCI if indicated) should be considered in patients with resuscitated cardiac arrest without diagnostic ST-segment elevation but with high suspicion of ongoing myocardial ischemia (Class IIa) [4]. Nevertheless, ACS is a peculiar situation in terms of thrombotic and hemorrhagic balance. Indeed, OHCA patients are at higher risk of thrombosis and bleeding due to potential resuscitation traumatism, invasive monitoring, and post-resuscitation syndrome [5]. There is no specific recommendation regarding anti-thrombotic therapy in this specific population. In general practice, the use of Glycoprotein IIb/IIIa inhibitors (GPI) is usually considered for bailout situations (large thrombus, slow- or no-reflow) or thrombotic complications in patients with ACS (Class IIa) [4], although this strategy has not been tested in a randomized trials. Nevertheless, the use of GPI is related to increased risk of bleeding, that could overcome potential benefit in high-bleeding risk populations such as OHCA patients. Indeed, data regarding the use of GPI in OHCA patients undergoing PCI is scarce [6]. Therefore, we sought to evaluate the benefit and safety of GPI use in OHCA patients requiring PCI.

Methods

Study design and population

This was an observational, single-center, retrospective study of consecutive patients treated for an OHCA from cardiac cause with PCI between January 2007 and December 2017, that was conducted at Cochin Hospital, an academic tertiary center. In this analysis, all

consecutive patients presenting with an OHCA from cardiac cause treated with PCI and stent implantation during the study period were included. Exclusion criteria included age<18-year-old, and patients that did not have stent implantation. Two groups were defined according to GPI administration. The study was conducted according to the Declaration of Helsinki. As this was a retrospective analysis conducted per institutional guidelines for data security and privacy, a waiver of consent was granted. Data were anonymized by authors prior to analysis.

Baseline and procedural characteristics

Baseline demographics, medical history, cardiac catheterization data and in-hospital outcomes were abstracted from medical charts. Patients were treated with aspirin and heparin prior to hospital admission or during the procedure. The use of GPI was at the operator's preference but usually considered for bailout situations (large thrombus, slow- or no-reflow) or thrombotic complications. Tirofiban and abciximab were the two GPI used, according to hospital protocol and recommended dosage. The arterial access site (femoral or other), although not recorded in the present analysis was mainly femoral due to local protocol but left at the operators' discretion. The use of clopidogrel, ticagrelor or prasugrel was also left at the operators' discretion. After PCI, all patients were transferred to Intensive Care Unit (ICU). Aspirin was administered intravenously during pre-hospital transfer when signs of ST-elevation myocardial infarction on electrocardiogram or per-procedure when not administered earlier. P2Y12 inhibitors were administered through nasogastric tube either per-procedure or upon arrival in ICU.

Clinical endpoints and definitions

The primary endpoints were the occurrence of in-hospital acute stent thrombosis and the incidence of in-hospital bleeding events. ST was defined according to the Academic Research

Consortium for trials involving stent [7]. A ST was *definite* when acute coronary syndrome with angiographic or pathological confirmation of thrombus was provided, *probable* when unexplained death within 30 days or MI involving target vessel territory without angiographic confirmation was diagnosed. In cardiac arrest patients, *probable* stent thrombosis was determined using serial troponin measurements, serial 12-lead ECGs and unexplained hemodynamic deterioration without other clear cause for cardiac arrest patients and without angiographic confirmation of stent thrombosis. Repeated coronary angiography was usually performed in the department in case of recurrent ST-segment elevation, abnormal troponin rise after the acute phase or hemodynamic degradation associated with ECG modifications. Bleedings complications were defined using the Bleeding Academic Research Consortium (BARC) [8]. Type 3 and 5 of BARC classification were considered. Type 3 encompassed: 3a: Overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding; 3b: overt bleeding plus hemoglobin drop ≥ 5 g/dL or cardiac tamponade or bleeding requiring surgical intervention for control or bleeding requiring intravenous vasoactive agents and 3c: Intracranial hemorrhage, subcategories confirmed by autopsy or imaging or lumbar puncture or intraocular bleed compromising vision. Type 5 included fatal bleeding, ie. 5a: probable fatal bleeding, no autopsy or imaging confirmation but clinically suspicious; 5b: Definite fatal bleeding overt bleeding or autopsy or imaging confirmation.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation when normally distributed and as median [inter-quartile range] otherwise. Categorical variables were expressed as count and percentage. The associations between categorical variables were assessed using a chi-square test (or Fisher exact test when appropriate) and continuous variables compared with Student t-test. Multivariate logistical regression was developed to assess the association

between baseline characteristics of interest (pre-specified patient, lesion and procedural variables) and the use of GPI. In addition, univariate and multivariate logistical regression were developed to assess the association between baseline characteristics of interest (pre-specified patient, lesion and procedural variables) including GPI use and the association with the occurrence of major bleeding. Candidate covariates that showed marginal associations to outcome on univariate testing ($p \leq 0.15$), up to a maximum of a tenth of the number of events, in order to prevent overfitting, were included in our multivariate analysis. Odds ratios (ORs) are presented with 95% confidence interval (CI). Statistical significance was defined at a level of $\alpha \leq 0.05$. Statistical analyses were carried out using SPSS package v23.0 (Chicago, IL, USA).

Results

Population and procedure

Between January 2007 and December 2017, 385 patients were treated with PCI following OHCA without reaching exclusion criteria (Figure 1). GPI were administrated in 41.3% of cases (159 patients). Patients baseline characteristics and clinical presentation are described in Table 1. 377 (97.9%) patients were comatose and benefited from mechanical ventilation under sedation. There was no major difference among the two populations. Between our two groups, patients in the GPI group had less hypertension (26.4% vs. 46.7%, $p < 0.001$) as well as less prior PCI (9.4% vs. 24.9%, $p < 0.001$). Initial clinical presentation also differed on two criteria, as GPI patients presented more often an initial shockable rhythm (96.3% vs. 76.8%, $p = 0.01$), and ST-segment elevation was more often present (83.9% vs. 64.6%, $p < 0.001$). Therapeutic hypothermia was performed in 86.0% of the patients over the first 24 hours according to local protocol.

Concerning procedural characteristics, the culprit coronary artery was more often the left anterior descending artery in the GPi group (64.7% vs. 53.1%, $p<0.0001$). GPi patients presented more often a TIMI 0 or 1 before PCI (79.9 % vs. 58.0%, $p<0.001$) and operators were more likely to perform thromboaspiration (63.9% vs. 28.9%, $p<0.001$). No reflow during procedure was also more often described in GPi patients (8.9% vs. 1.8%, $p=0.001$). Regarding peri-procedural medical treatment, antiplatelet therapy was well balanced between the two groups. Procedural characteristics are summarized in Table 2.

Determinants of Glycoprotein IIb/IIIa inhibitor usage

GPi were used in 41.3% of patients. Multivariate analyses of factors associated with administration of GPi are showed in Table 3. Using multivariate regression, younger age (OR 0.98(0.96-1.00), $p=0.04$), the absence of prior PCI (OR: 0.49 (0.25-0.96), $p=0.04$), thromboaspiration (OR: 2.89 (1.78-4.70), $p<0.0001$) and a TIMI 0 or 1 flow before PCI (OR: 2.01 (1.17-3.45), $p=0.01$) were the only parameters associated with use of GPi during the procedure. Gpi use was consistant over the study timeframe (Supplemental Figure 1).

Outcomes, thrombotic and bleeding events

In-hospital mortality was high, up to 47.8% of the patients. Bleeding stage 3 or 5 of BARC classification affected 22.1% of patients, and acute stent thrombosis 9.1% of patients. In-hospital outcomes are summarized in Table 4 and Figure 2. Bleeding events rates were significantly different between the two population. GPi patients were more likely to present any bleeding complications (33.3% vs. 19.6%, $p=0.002$), as well as BARC 3-5 bleedings (28.3% vs. 16.8%, $p=0.007$). On the other hand, there were no significant differences concerning ST or in-hospital mortality ($p=0.10$ and $p=0.68$, respectively).

Bleeding events predictors

Uni- and multi-variate analysis of risk factors associated with major bleeding (BARC 3-5 of the BARC classification) are described in Table 5. Using univariate analysis, dual antiplatelet therapy associating aspirin to a more potent P2Y₁₂ inhibitor (ticagrelor or prasugrel) (OR 1.48 (0.91-2.41), p=0.12), the use of thromboaspiration (OR: 1.45 (0.90-2.37), p=0.13), low-flow duration (OR: 1.01 (1.00-1.03), p=0.08), and total length of implanted stent (OR: 0.99 (0.97-1.00), p=0.10) tended to be associated with increased major bleeding events. The use of GPi (OR: 1.95 (1.20-3.19), p=0.007) and mechanical support devices (ECMO, Impella or IABP) (OR:1.86 (1.12-3.10), p=0.02) were the only significant predictors of major bleeding. Using multivariate analysis, the administration of GPi remained a significant predictor of higher risk of major bleeding event (OR: 1.81 (1.06-3.08), p=0.03), as well as mechanical support device use (OR: 2.03 (1.14-3.62), p=0.02) and dual antiplatelet therapy associating aspirin to a more potent P2Y₁₂ inhibitor (ticagrelor or prasugrel) (OR: 1.99 (1.15-3.46), p=0.01).

Discussion

The main finding of this study was that the use of GPi in the specific context of OHCA patients associated with ACS is statistically associated with increased risk of bleeding events (any or major), without any significant differences for stent thromboses or in-hospital mortality.

Glycoprotein IIb/IIIa receptor activation is the common final link of platelet aggregation. Several studies suggest that the use of GPi may reduce thrombotic complications in patients undergoing primary PCI [9]. However, the fact that inflammatory pro-thrombotic environment in ACS leading to cardiac arrest was significantly different than in others has

been recently pointed at. Empana et al showed higher concentrations of endothelial-derived micro particles in sudden cardiac death due to acute coronary occlusion compared with acute myocardial infarction with STEMI without rhythmic disturbances suggesting different patterns of acute coronary occlusion [10]. Nevertheless, a more recent study analyzed the thrombus with a quantitative method using scanning electron microscopy did not find any differences of composition between intra-coronary thrombi of patients presenting with STEMI leading to sudden cardiac death or not [11]. In this study time from symptom onset to coronary reperfusion seems to be the strongest factor influencing thrombus composition in myocardial infarction. Use of GPI showed empiric benefit concerning thrombotic events following PCI [4] though data lack in this in this specific context of ACS leading to cardiac-arrest. In our study, we noted a numerically higher ST rate in the Gpi group. We believe that this was due to two main factors. First, the fact that patients in the Gpi group had higher thrombotic burden is of importance to note as these patients might be at greater risk of ST. Indeed, we cannot ascertain that patients with higher thrombus burden might not have benefited from GPI, as such therapy has been proven to reduce thrombus burden [12]. Nevertheless, recent analysis demonstrated low ischemic benefit on top of P2Y12 inhibitors [13,14]. If routine Gpi use should not be advised in OHCA patients, randomized controlled studies with Gpi, cangrelor and oral P2Y12 inhibitors could be of interest in such patients. Second, the fact that Gpi patients experienced more major bleedings could result in a need to interrupt other antithrombotic therapies and result in ST. Indeed, in stable patients who experienced both bleeding and ischemic events, bleeding events were reported to occur first in most patients [15].

Our study showed an increased risk of bleeding events (any events, $p=0.002$ and BARC 3 or 5 events, $p=0.007$) in the GPI groups without any increased of ST or in-hospital death ($p=0.10$ and $p=0.68$, respectively). These results are consistent with precedent data. In a single center

260 observational study, Jimenez-Britez *et al.* showed that the incidence of any bleeding (64.7%
261 vs. 14.8%, $p<0.0001$) and major bleeding (41.1% vs. 3.7%, $p<0.0001$) was significantly
262 higher in patients receiving GPi. Their definition of thrombotic events contained ST but also
263 deep vein thrombosis and pulmonary thrombosis and there were no significant differences
264 between the two groups ($p=0.76$). In-hospital mortality was not significantly different either
265 (24% vs. 35.2%, $p=0.39$) [6]. To our knowledge, our study is the largest reported,
266 demonstrating that GPi could increase bleeding events without any difference on in-hospital
267 or stent thrombosis. Interestingly, even if not statistically relevant, stent thrombosis was
268 numerically higher in GPi use. In the 19 patients with GPi who presented ST, 6 also presented
269 a major bleeding complication according to BARC criteria (31.6%). In these cases, an early
270 discontinuation of the double antiplatelet therapy may have led to an increased risk of ST
271 which would have been related to GPi use in the first place. The hypothesis would need
272 further investigation with more important cohorts of OHCA patients presenting with ACS.

273 In the population of OHCA patients with ACS, cardiogenic shock as well as reduced body
274 temperature impacts platelet reactivity. In a prospective observational non-randomized study
275 including 25 resuscitated patients, lowest inhibitory effects of both aspirin and P2Y12
276 inhibitors was shown on day 3[16]. The authors emphasized that intravenous aspirin and
277 P2Y12 inhibitors might supply a more predictable and stable platelet inhibition. However, in
278 another study comparing the effects of clopidogrel and GPi on platelet reactivity in patients
279 resuscitated from OHCA and undergoing PCI and hypothermia, the antiplatelet effect of
280 clopidogrel measured by VerifyNow was significantly lower in the post-cardiac arrest group,
281 close to zero with an increase to only around 10% after 48 hours. In the other hand, patients
282 receiving GPi showed profound platelet inhibition measured by both VerifyNow I Ib/IIIa and
283 Multiplate TRAP tests for at least 22 hours after administration. These results showed that
284 Clopidogrel loading does not significantly affect platelet function during the first 48 hours.

This is in contrast with eptifibatide which produces profound platelet inhibition, and may be used to bridge insufficient inhibition by clopidogrel [17]. Nevertheless, a new P2Y₁₂ inhibitor has been recently added to the arsenal in patient presenting for ACS in a cardiac-arrest context. Indeed, cangrelor belongs to a novel chemical class, cyclopentyl triazolopyrimidine, and is a direct, reversibly binding P2Y₁₂ inhibitor with a plasma half-life of 12 h. It has been shown to provide effective platelet inhibition and is an appealing alternative to GPI in this context [18]. Its efficacy has been assessed in three randomized controlled trials enrolling patients with PCI for stable angina or ACS against clopidogrel loading or placebo [18]. However, the comparative efficacy and safety of routine early oral P2Y₁₂ inhibitor administration vs. the use of cangrelor in the catheterization laboratory in patients with ACS undergoing invasive management deserves further investigation. Nevertheless, OHCA patients in shock and treated with hypothermia therapy remains a specific population with different inflammatory pro-thrombotic environment and the standardized medication could be less effective. Further studies are warranted to confirm the mechanisms of higher thrombotic events, as well as to assess the appropriate management of these patients. In addition, inadequate platelet inhibition is only one component of ST pathogenesis as an individual's susceptibility to ST is multifactorial involving clinical factors, endothelial biology, inflammatory reaction, blood rheology, platelet reactivity, clotting factors, physical and mechanical properties of the stent [19]. Therefore all efforts should be done to reduce any potential ST trigger, such as appropriate stenting technique, with the help, if needed of intravascular imaging; inflammatory reaction control and other manageable factors such as hyperglycemia or hypoperfusion.

The present study has several limitations that need to be acknowledged. The results must be interpreted with caution, as this is a single-center non-randomized study with a relatively

310 small sample size. Thus, the differences in baseline or procedural characteristics might have
311 impacted on the final results of the study. Nevertheless, to our knowledge, our study is the
312 largest analyzing the safety of GPi in OHCA patients. Among them, the higher thrombotic
313 burden in the patients receiving GPi might probably reflect a more pro-thrombotic
314 environment that could lead to an increased risk of stent thrombosis. Nonetheless, these
315 limitations may potentially impact on thrombotic but not hemorrhagic events. The study
316 included patients that were treated over a long period (10 years). Indeed, the use of
317 clopidogrel was superior between 2007 and 2012; conversely ticagrelor and prasugrel were
318 more used after 2012. In addition, mechanical support devices such as IABP and Impella were
319 more often used in the first 5 years of the study, due to in-hospital management protocols.
320 However there were no difference in mortality between these two periods (2007-2012:
321 45.1% ; 2013-2017 : 41.9%; $p=0.27$). In addition, although therapeutic hypothermia was
322 performed in the vast majority of the patients, the depth of hypothermia was not recorded.
323 The choice of the P2Y12 inhibitor and GPi use was not randomized and left to the discretion
324 of the clinician, therefore introducing potential bias. In addition, type, dose, and duration of
325 GPi are not detailed in the present analysis, which can hamper detailed analysis of GPi
326 administration. Also, there was an evolution in stent thrombosis rates during the study period
327 with the use of bare metal stents; first, second and third generation of drug-eluting stents, as
328 well as an evolution in the access site (ie, radial vs femoral) which were not recorded in the
329 present analysis. Due to high mortality rate, ST might have been missed in a number of
330 patients. Nevertheless, repeated coronary angiography was usually performed in the
331 department in case of recurrent ST-segment elevation, abnormal troponin rise after the acute
332 phase or hemodynamic degradation associated with ECG modifications, factors usually
333 associated with ST. In addition, ST rates should have affected both groups and might not be

in favor of one group or the other. Finally, the rates of any bleeding might have been underreported as they are rarely mentioned in medical charts.

Conclusion

In this study, the use of GPI in patients with ACS in a context of OHCA was associated with an increased risk of any bleeding or major bleeding events according to BARC criteria, without any significant differences concerning the risk of stent thrombosis or in-hospital death. Further studies are required to insure the safety of GPI in the very specific population of patient undergoing PCI following a cardiac arrest.

Figure Legend

Figure 1: Study Flowchart. *Abbreviations: CCU: critical care unit; OHCA: out of hospital cardiac arrest; GpIIbIIIa: Glycoprotein IIbIIIa.*

Figure 2: Outcomes according to GPi use. *ST=stent thrombosis; GPi=Glycoprotein IIb/IIIa inhibitors*

Supplementary Figure 1: Gpi use over time.

Tables

Table 1: Baseline characteristics, clinical presentation and pre-hospital management.

Abbreviations: BMI: Body mass index, PCI: Percutaneous coronary intervention, EES:

External electric shock; LVEF: left ventricular ejection fraction

	GPI (n : 159)	Non GPI (n : 226)	p value
Age, years, mean \pm SD	57.8 \pm 12.4	62.9 \pm 12.1	0.23
Male, no. (%)	126 (79.2%)	169 (74.8%)	0.31
BMI, mean \pm SD	133 (26.0 \pm 4.1)	26.7 \pm 5.0	0.70
Smoking, no. (%)	105 (66.0%)	142 (62.8%)	0.52
Hypertension, no. (%)	42 (26.4%)	110 (48.7%)	<0.001
Diabetes mellitus, no. (%)	20 (12.6%)	44 (19.5%)	0.07
Hypercholesterolemia, no. (%)	37 (23.3%)	72 (31.9%)	0.07
Family history of coronary artery disease, no. (%)	8 (5.0%)	19 (8.4%)	0.20
Previous PCI, no. (%)	15 (9.4%)	56 (24.9%)	<0.001
Anticoagulant treatment, no. (%)	8 (5.0%)	12 (5.3%)	0.90
Initial shockable rhythm, no. (%)	138 (87.3%)	172 (76.8%)	0.01
Present witness, no. (%)	154 (97.5%)	217 (96.0%)	0.44
Resuscitation by the witness, no. (%)	107 (68.2%)	143 (63.6%)	0.35
No Flow time, min, Median (IR)	2 (0 – 5)	2 (0 – 7)	0.29
Low Flow time, min, Median (IR)	15 (10 – 28)	20 (10 – 25)	0.14
Mechanical ventilation	156 (98.1%)	221 (97.8%)	0.99
Therapeutic hypothermia	135 (84.9%)	196 (86.7%)	0.61
ST-segment elevation myocardial infarction, no. (%)	132 (83.0%)	146 (64.6%)	<0.001
Number of EES, mean \pm SD	1.1 \pm 1.4	1.0 \pm 1.7	0.10
Adrenaline injection, no. (%)	86 (54.4%)	120 (54.1%)	0.94
Morphine injection, no. (%)	158 (99.4%)	224 (99.1%)	0.78
LVEF, %, mean \pm SD	36.4 \pm 14.1	36.8 \pm 14.7	0.81

Table 2: Procedural characteristics. *Abbreviations: IABP: intra-aortic balloon pump, ECMO: extra-corporeal mechanical oxygenation, TIMI: thrombolysis in myocardial infarction, PCI: percutaneous coronary intervention, LAD: left descending artery, LCX: left circumflex artery, RCA: Right coronary artery.*

	GPi (n: 159)	Non GPi (n: 226)	p value
Antiplatelets administered before or during catheterization procedure, no. (%)			
Aspirine + Clopidogrel	78 (49.1%)	114 (50.4%)	0.79
Aspirine + Ticagrelor or Prasugrel	70 (44.0%)	91 (40.3%)	0.46
IABP, no. (%)	43 (27.0%)	41 (18.1%)	0.04
Impella implantation, no. (%)	10 (6.3%)	11 (4.9%)	0.55
ECMO implantation, no. (%)	8 (5.2%)	13 (5.8%)	0.78
Thromboaspiration, no. (%)	101 (63.9%)	65 (28.9%)	<0.0001
TIMI flow 0 or 1 before PCI, no. (%)	127 (79.9%)	131 (58.0%)	<0.0001
TIMI flow 3 after PCI, no. (%)	148 (93.1%)	218 (96.5%)	0.13
Bifurcation lesion, no. (%)	39 (24.5%)	61 (26.9%)	0.63
Culprit coronary artery, no. (%)			
LAD	103 (64.7%)	120 (53.1%)	0.02
LCX	24 (15.1%)	47 (20.8%)	0.16
RCA	31 (19.5%)	57 (26.1%)	0.19
Other	1 (0.6%)	2 (0.9%)	0.78
No reflow, no. (%)	14 (8.9%)	4 (1.8%)	0.001
Total length of implanted stent, mm, mean \pm (SD)	26.6 \pm 13.8	30.7 \pm 21.1	0.04
Switch of antiplatelets, no. (%)	24 (15.1%)	52 (23.0%)	0.06

Table 3: Uni and multivariate analysis of factors associated with the use of Gpi.
Abbreviations: Same as Table 1 and 2.

Univariate predictors	Odds ratio	95% CI	p value
Age, years, mean \pm SD	0.97	0.95-0.98	<0.0001
Male, no. (%)	1.3	0.79-2.10	0.31
BMI, mean \pm SD	0.97	0.92-1.02	0.22
Anticoagulant treatment, no. (%)	0.94	0.38-2.36	0.90
Initial shockable rhythm, no. (%)	2.09	1.19-3.66	0.01
IABP use, no. (%)	1.67	1.03-2.72	0.04
Impella implantation, no. (%)	1.31	0.54-3.17	0.55
ECMO implantation, no. (%)	0.88	0.36-2.17	0.78
Thromboaspiration, no. (%)	4.36	2.83-6.73	<0.0001
TIMI flow 0 or 1 before PCI, no. (%)	2.88	1.80-4.60	<0.0001
TIMI flow 3 after PCI, no. (%)	0.79	0.58-1.08	0.14
Bifurcation lesion, no. (%)	0.89	0.57-1.40	0.63
No reflow, no. (%)	5.40	1.74-16.72	0.003
Total length of implanted stent, mm, mean \pm (SD)	0.99	0.98-1.00	0.04
Therapeutic hypothermia	0.86	0.48-1.54	0.61
Multivariate predictors	Odds ratio	95% CI	p value
Age, years, mean \pm SD	0.98	0.96-1.00	0.04
Previous PCI, no. (%)	0.49	0.25-0.96	0.04
Initial shockable rhythm, no. (%)	1.20	0.63-2.30	0.58
IABP use, no. (%)	1.20	0.69-2.08	0.53
Thromboaspiration, no. (%)	2.89	1.78-4.70	<0.0001
TIMI flow 0 or 1 before PCI, no. (%)	2.01	1.17-3.45	0.01
TIMI flow 3 after PCI, no. (%)	1.13	0.70-1.83	0.62
No reflow, no. (%)	3.78	0.81-17.62	0.09
Total length of implanted stent, mm, mean \pm (SD)	0.99	0.98-1.01	0.25

441 Table 4: Clinical outcomes. *Abbreviation: BARC: Bleeding Academic Research Consortium*
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	GPI (n: 159)	Non GPI (n: 226)	<i>p</i> value
Any bleeding, no. (%)	53 (33.3%)	44 (19.6%)	0.002
Major bleeding (BARC 3-5), no. (%)	45 (28.3%)	38 (16.8%)	0.007
Stent thrombosis, no. (%)	19 (11.9%)	16 (7.1%)	0.10
In-hospital mortality, no. (%)	74 (47.1%)	110 (49.3%)	0.68

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Table 5: Uni- and multivariate analysis of factors associated with major (BARC 3-5) bleedings. *Abbreviations: Same as Table 1,2 and 4.*

Univariate predictors	Odds ratio	95% CI	p value
BMI, mean \pm SD	0.96	0.90-1.03	0.26
Smoking, no. (%)	0.76	0.46-1.25	0.27
Antiplatelets administered before or during catheterization procedure, no. (%)			
Aspirine + Clopidogrel	0.72	0.44-1.17	0.18
Aspirine + Ticagrelor or Prasugrel	1.48	0.91-2.41	0.12
GpIIb/IIIa inhibitors use, no. (%)	1.95	1.20-3.19	0.007
Thromboaspiration, no. (%)	1.45	0.90-2.37	0.13
Total length of implanted stent, mm, mean \pm (SD)	0.99	0.97-1.00	0.10
Switch of antiplatelets, no. (%)	1.28	0.71-2.30	0.42
Therapeutic hypothermia	0.85	0.43-1.67	0.63
Anticoagulation use	0.90	0.29-2.77	0.86
No-Flow duration	0.97	0.91-1.02	0.23
Low-Flow duration	1.01	1.00-1.03	0.08
Mechanical support device (ECMO, Impella or IABP)	1.86	1.12-3.10	0.02
Multivariate predictors	Odds ratio	95% CI	p value
Aspirine + Ticagrelor or Prasugrel, no. (%)	1.99	1.15-3.46	0.01
GpIIb/IIIa inhibitors use, no. (%)	1.81	1.06-3.08	0.03
Thromboaspiration, no. (%)	1.15	0.66-2.01	0.61
Total length of implanted stent, mm, mean \pm (SD)	0.99	0.97-1.00	0.12
Low-Flow duration	1.01	1.00-1.03	0.07
Mechanical support device (ECMO, Impella or IABP)	2.03	1.14-3.62	0.02

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