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

3
4 Fabien Picard, MD, MSc^{1,2,3}; Anastasia Sokoloff, MD¹; Vincent Pham, MD¹; Marine
5 Diefenbronn, MD¹; Driss Laghlam, MD¹; Gabriel Seret, MD¹; Olivier Varenne, MD, PhD^{1,2};
6 Florence Dumas MD, PhD^{2,3,4}; Alain Cariou, MD, PhD^{2,3,5}.

7
8 **Affiliations:**

9 1: Department of Cardiology, Cochin Hospital, Hôpitaux Universitaire Paris Centre,
10 Assistance Publique des Hôpitaux de Paris, Paris, France
11 2: Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris, France
12 3 : INSERM U970, Paris Cardiovascular Research Center (PARCC), European Georges
13 Pompidou Hospital, Paris, France
14 4 : Emergency Department, Cochin Hospital, Hôpitaux Universitaire Paris Centre, Assistance
15 Publique des Hôpitaux de Paris, Paris, France
16 5 : Medical Intensive Care Unit, Cochin Hospital, Hôpitaux Universitaire Paris Centre,
17 Assistance Publique des Hôpitaux de Paris, Paris, France

18
19 **Address for correspondence:** Fabien Picard, Cardiology Department, Cochin Hospital,
20 Hôpitaux Universitaire Paris Centre, Assistance Publique des Hôpitaux de Paris, 27 rue du
21 Faubourg Saint-Jacques, 75014 Paris, France; Fax: +33 158411666; Phone: +33 158412750;
22 E-mail: Fabien.picard@aphp.fr

23
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25
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31
32 **Wordcount: 3018**

35 **Abstract**

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

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

42 **Methods and Results:** Between January 2007 and December 2017, we retrospectively
43 included all consecutive patients treated with PCI for an OHCA from cardiac cause. Clinical,
44 procedural data and in-hospital outcomes were collected. Three hundred and eighty-five
45 patients were included. GPI were administrated in 41.3% of cases (159 patients). Patients who
46 received GPI were younger, had less prior PCI, more often a TIMI 0 or 1 flow before PCI and
47 thromboaspiration use. There were no differences regarding in-hospital definite stent
48 thrombosis among the two groups (11.9% in the GPI group vs 7.1% in the non-GPI group,
49 $p=0.10$) or in-hospital mortality (48.6% vs 49.3%, $p=0.68$). The incidence of any bleeding
50 (33.3% vs. 19.6%; $p=0.002$), and major bleeding (BARC 3-5) (21.9% vs. 16.8%; $p=0.007$)
51 was significantly higher in patients receiving GPI. Indeed, using multivariate analysis, GPI
52 use was predictor of major bleeding (OR: 1.81; 95% CI: 1.06-3.08; $p=0.03$).

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

56

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

59 **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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86 **Introduction**

87
88 Acute coronary syndromes (ACS) are the leading cause of cardiac arrest [1]. European
89 guidelines recommend urgent coronary angiography in a view for primary percutaneous
90 coronary intervention (PCI) in survivors of out-of-hospital cardiac arrest (OHCA) [1-3]. A
91 primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG
92 consistent with STEMI (Class I), and urgent angiography (and PCI if indicated) should be
93 considered in patients with resuscitated cardiac arrest without diagnostic ST-segment
94 elevation but with high suspicion of ongoing myocardial ischemia (Class IIa) [4].
95 Nevertheless, ACS is a peculiar situation in terms of thrombotic and hemorrhagic balance.
96 Indeed, OHCA patients are at higher risk of thrombosis and bleeding due to potential
97 resuscitation traumatism, invasive monitoring, and post-resuscitation syndrome [5]. There is
98 no specific recommendation regarding anti-thrombotic therapy in this specific population. In
99 general practice, the use of Glycoprotein IIb/IIIa inhibitors (GPi) is usually considered for
100 bailout situations (large thrombus, slow- or no-reflow) or thrombotic complications in
101 patients with ACS (Class IIa) [4], although this strategy has not been tested in a randomized
102 trials. Nevertheless, the use of GPi is related to increased risk of bleeding, that could
103 overcome potential benefit in high-bleeding risk populations such as OHCA patients. Indeed,
104 data regarding the use of GPi in OHCA patients undergoing PCI is scarce [6]. Therefore, we
105 sought to evaluate the benefit and safety of GPi use in OHCA patients requiring PCI.

106
107 **Methods**

108 *Study design and population*

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

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

118

119 ***Baseline and procedural characteristics***

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

133

134 ***Clinical endpoints and definitions***

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

137 Consortium for trials involving stent [7]. A ST was *definite* when acute coronary syndrome
138 with angiographic or pathological confirmation of thrombus was provided, *probable* when
139 unexplained death within 30 days or MI involving target vessel territory without angiographic
140 confirmation was diagnosed. In cardiac arrest patients, *probable* stent thrombosis was
141 determined using serial troponin measurements, serial 12-lead ECGs and unexplained
142 hemodynamic deterioration without other clear cause for cardiac arrest patients and without
143 angiographic confirmation of stent thrombosis. Repeated coronary angiography was usually
144 performed in the department in case of recurrent ST-segment elevation, abnormal troponin
145 rise after the acute phase or hemodynamic degradation associated with ECG modifications.
146 Bleedings complications were defined using the Bleeding Academic Research Consortium
147 (BARC) [8]. Type 3 and 5 of BARC classification were considered. Type 3 encompassed: 3a:
148 Overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding;
149 3b: overt bleeding plus hemoglobin drop ≥ 5 g/dL or cardiac tamponade or bleeding requiring
150 surgical intervention for control or bleeding requiring intravenous vasoactive agents and 3c:
151 Intracranial hemorrhage, subcategories confirmed by autopsy or imaging or lumbar puncture
152 or intraocular bleed compromising vision. Type 5 included fatal bleeding, ie. 5a: probable
153 fatal bleeding, no autopsy or imaging confirmation but clinically suspicious; 5b: Definite fatal
154 bleeding overt bleeding or autopsy or imaging confirmation.

155

156 ***Statistical analysis***

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

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

172

173 **Results**

174 *Population and procedure*

175 Between January 2007 and December 2017, 385 patients were treated with PCI following
176 OHCA without reaching exclusion criteria (Figure 1). GPi were administrated in 41.3% of
177 cases (159 patients). Patients baseline characteristics and clinical presentation are described in
178 Table 1. 377 (97.9%) patients were comatose and benefited from mechanical ventilation
179 under sedation. There was no major difference among the two populations. Between our two
180 groups, patients in the GPi group had less hypertension (26.4% vs. 46.7%, $p < 0.001$) as well as
181 less prior PCI (9.4% vs. 24.9%, $p < 0.001$). Initial clinical presentation also differed on two
182 criteria, as GPi patients presented more often an initial shockable rhythm (96.3% vs. 76.8%,
183 $p = 0.01$), and ST-segment elevation was more often present (83.9% vs. 64.6%, $p < 0.001$).
184 Therapeutic hypothermia was performed in 86.0% of the patients over the first 24 hours
185 according to local protocol.

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

193

194 ***Determinants of Glycoprotein IIb/IIIa inhibitor usage***

195 GPi were used in 41.3% of patients. Multivariate analyses of factors associated with
196 administration of GPi are showed in Table 3. Using multivariate regression, younger age
197 (OR 0.98(0.96-1.00), $p=0.04$), the absence of prior PCI (OR: 0.49 (0.25-0.96), $p=0.04$),
198 thromboaspiration (OR: 2.89 (1.78-4.70), $p<0.0001$) and a TIMI 0 or 1 flow before PCI (OR:
199 2.01 (1.17-3.45), $p=0.01$) were the only parameters associated with use of GPi during the
200 procedure. Gpi use was consistant over the study timeframe (Supplemental Figure 1).

201

202 ***Outcomes, thrombotic and bleeding events***

203 In-hospital mortality was high, up to 47.8% of the patients. Bleeding stage 3 or 5 of BARC
204 classification affected 22.1% of patients, and acute stent thrombosis 9.1% of patients. In-
205 hospital outcomes are summarized in Table 4 and Figure 2. Bleeding events rates were
206 significantly different between the two population. GPi patients were more likely to present
207 any bleeding complications (33.3% vs. 19.6%, $p=0.002$), as well as BARC 3-5 bleedings
208 (28.3% vs. 16.8%, $p=0.007$). On the other hand, there were no significant differences
209 concerning ST or in-hospital mortality ($p=0.10$ and $p=0.68$, respectively).

210

211 ***Bleeding events predictors***

212 Uni- and multi-variate analysis of risk factors associated with major bleeding (BARC 3-5 of
213 the BARC classification) are described in Table 5. Using univariate analysis, dual antiplatelet
214 therapy associating aspirin to a more potent P2Y12 inhibitor (ticagrelor or prasugrel) (OR
215 1.48 (0.91-2.41), p=0.12), the use of thromboaspiration (OR: 1.45 (0.90-2.37), p=0.13), low-
216 flow duration (OR: 1.01 (1.00-1.03), p=0.08), and total length of implanted stent (OR: 0.99
217 (0.97-1.00), p=0.10) tended to be associated with increased major bleeding events. The use of
218 GPi (OR: 1.95 (1.20-3.19), p=0.007) and mechanical support devices (ECMO, Impella or
219 IABP) (OR:1.86 (1.12-3.10), p=0.02) were the only significant predictors of major bleeding.
220 Using multivariate analysis, the administration of GPi remained a significant predictor of
221 higher risk of major bleeding event (OR: 1.81 (1.06-3.08), p=0.03), as well as mechanical
222 support device use (OR: 2.03 (1.14-3.62), p=0.02) and dual antiplatelet therapy associating
223 aspirin to a more potent P2Y12 inhibitor (ticagrelor or prasugrel) (OR: 1.99 (1.15-3.46),
224 p=0.01).

225

226 **Discussion**

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

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

235 been recently pointed at. Empana et al showed higher concentrations of endothelial-derived
236 micro particles in sudden cardiac death due to acute coronary occlusion compared with acute
237 myocardial infarction with STEMI without rhythmic disturbances suggesting different
238 patterns of acute coronary occlusion [10]. Nevertheless, a more recent study analyzed the
239 thrombus with a quantitative method using scanning electron microscopy did not find any
240 differences of composition between intra-coronary thrombi of patients presenting with
241 STEMI leading to sudden cardiac death or not [11]. In this study time from symptom onset to
242 coronary reperfusion seems to be the strongest factor influencing thrombus composition in
243 myocardial infarction. Use of GPI showed empiric benefit concerning thrombotic events
244 following PCI [4] though data lack in this in this specific context of ACS leading to cardiac-
245 arrest. In our study, we noted a numerically higher ST rate in the Gpi group. We believe that
246 this was due to two main factors. First, the fact that patients in the Gpi group had higher
247 thrombotic burden is of importance to note as these patients might be at greater risk of ST.
248 Indeed, we cannot ascertain that patients with higher thrombus burden might not have
249 benefited from GPI, as such therapy has been proven to reduce thrombus burden [12].
250 Nevertheless, recent analysis demonstrated low ischemic benefit on top of P2Y12 inhibitors
251 [13,14]. If routine Gpi use should not be advised in OHCA patients, randomized controlled
252 studies with Gpi, cangrelor and oral P2Y12 inhibitors could be of interest in such patients.
253 Second, the fact that Gpi patients experienced more major bleedings could result in a need to
254 interrupt other antithrombotic therapies and result in ST. Indeed, in stable patients who
255 experienced both bleeding and ischemic events, bleeding events were reported to occur first in
256 most patients [15].

257 Our study showed an increased risk of bleeding events (any events, $p=0.002$ and BARC 3 or 5
258 events, $p=0.007$) in the GPI groups without any increased of ST or in-hospital death ($p=0.10$
259 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 IIB/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.

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

307

308 The present study has several limitations that need to be acknowledged. The results must be
309 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

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

336

337 **Conclusion**

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

343

344 **Figure Legend**

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

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

349 **Supplementary Figure 1: Gpi use over time.**

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369 **Tables**

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

371 *Abbreviations: BMI: Body mass index, PCI: Percutaneous coronary intervention, EES:*372 *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 |

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385 Table 2: Procedural characteristics. *Abbreviations: IABP: intra-aortic balloon pump, ECMO:*
 386 *extra-corporeal mechanical oxygenation, TIMI: thrombolysis in myocardial infarction, PCI:*
 387 *percutaneous coronary intervention, LAD: left descending artery, LCX: left circumflex artery,*
 388 *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 ± (SD) | 26.6 ± 13.8 | 30.7 ± 21.1 | 0.04 |
| Switch of antiplatelets, no. (%) | 24 (15.1%) | 52 (23.0%) | 0.06 |

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413 Table 3: Uni and multivariate analysis of factors associated with the use of Gpi.
 414 *Abbreviations: Same as Table 1 and 2.*
 415

| Univariate predictors | Odds ratio | 95% CI | p value |
|---|-------------|-------------------|-------------------|
| Age, years, mean ± SD | 0.97 | 0.95-0.98 | <0.0001 |
| Male, no. (%) | 1.3 | 0.79-2.10 | 0.31 |
| BMI, mean ± 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 ± (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 ± 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 ± (SD) | 0.99 | 0.98-1.01 | 0.25 |

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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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486 Table 5: Uni- and multivariate analysis of factors associated with major (BARC 3-5)
 487 bleedings. *Abbreviations: Same as Table 1,2 and 4.*
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| Univariate predictors | Odds ratio | 95% CI | p value |
|--|-------------|------------------|--------------|
| BMI, mean ± 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 ± (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 ± (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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- 506 [1] Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, et al. European
507 Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-
508 resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for
509 Resuscitation 2015. *Resuscitation* 2015;95:202–22. doi:10.1016/j.resuscitation.2015.07.018.
- 510 [2] Bougouin W, Dumas F, Karam N, Maupain C, Marijon E, Lamhaut L, et al. Should We
511 Perform an Immediate Coronary Angiogram in All Patients After Cardiac Arrest?: Insights
512 From a Large French Registry. *JACC Cardiovasc Interv* 2018;11:249–56.
513 doi:10.1016/j.jcin.2017.09.011.
- 514 [3] Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, Olivecrona GK, et al. Invasive coronary
515 treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the
516 European association for percutaneous cardiovascular interventions (EAPCI)/stent for life
517 (SFL) groups. *EuroIntervention*, vol. 10, 2014, pp. 31–7. doi:10.4244/EIJV10I1A7.
- 518 [4] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC
519 Guidelines for the management of acute myocardial infarction in patients presenting with ST-
520 segment elevation: The Task Force for the management of acute myocardial infarction in
521 patients presenting with ST-segment elevation of the European Society of Cardiology (ESC).
522 *European Heart Journal* 2018;39:119–77. doi:10.1093/eurheartj/ehx393.
- 523 [5] Picard F, Llitjos J-F, Diefenbronn M, Laghnam D, Seret G, Sokoloff A, et al. The balance of
524 thrombosis and hemorrhage in STEMI patients with or without associated cardiac arrest: An
525 observational study. *Resuscitation* 2019;145:83–90. doi:10.1016/j.resuscitation.2019.10.022.
- 526 [6] Jiménez-Brítez G, Freixa X, Flores E, Penela D, Hernandez-Enriquez M, San Antonio R, et
527 al. Safety of glycoprotein IIb/IIIa inhibitors in patients under therapeutic hypothermia
528 admitted for an acute coronary syndrome. *Resuscitation* 2016;106:108–12.
529 doi:10.1016/j.resuscitation.2016.06.031.
- 530 [7] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, et al. Clinical end
531 points in coronary stent trials: a case for standardized definitions. *Circulation*, vol. 115,
532 American Heart Association, Inc; 2007, pp. 2344–51.
533 doi:10.1161/CIRCULATIONAHA.106.685313.
- 534 [8] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized
535 Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the
536 Bleeding Academic Research Consortium. *Circulation* 2011;123:2736–47.
537 doi:10.1161/CIRCULATIONAHA.110.009449.
- 538 [9] Boersma E, Harrington RA, Moliterno DJ, White H, Thérout P, Van de Werf F, et al.
539 Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all
540 major randomised clinical trials. *The Lancet* 2002;359:189–98. doi:10.1016/S0140-
541 6736(02)07442-1.
- 542 [10] Empana J-P, Boulanger CM, Tafflet M, Renard JM, Leroyer AS, Varenne O, et al.
543 Microparticles and sudden cardiac death due to coronary occlusion. The TIDE (Thrombus
544 and Inflammation in sudden DEath) study. *European Heart Journal: Acute Cardiovascular
545 Care* 2015;4:28–36. doi:10.1177/2048872614538404.
- 546 [11] Silvain J, Collet J-P, Guedeney P, Varenne O, Nagaswami C, Maupain C, et al. Thrombus
547 composition in sudden cardiac death from acute myocardial infarction. *Resuscitation*
548 2017;113:108–14. doi:10.1016/j.resuscitation.2017.01.030.
- 549 [12] Capodanno D, Milluzzo RP, Angiolillo DJ. Intravenous antiplatelet therapies (glycoprotein
550 IIb/IIIa receptor inhibitors and cangrelor) in percutaneous coronary intervention: from
551 pharmacology to indications for clinical use. *Ther Adv Cardiovasc Dis*
552 2019;13:1753944719893274. doi:10.1177/1753944719893274.
- 553 [13] Ibrahim H, Kaltenbach LA, Hess CN, Recchia T, Effron MB, Stone GW, et al. Glycoprotein
554 IIb/IIIa inhibitor use in patients with acute myocardial infarction undergoing PCI: Insights
555 from the TRANSLATE ACS study. *Catheter Cardiovasc Interv* 2019;93:E204–10.
556 doi:10.1002/ccd.27816.

- 557 [14] Tavenier AH, Hermanides RS, Fabris E, Lapostolle F, Silvain J, Berg Ten JM, et al. Efficacy
558 and Safety of Glycoprotein IIb/IIIa Inhibitors on Top of Ticagrelor in STEMI: A Subanalysis
559 of the ATLANTIC Trial. *Thromb Haemost* 2020;120:65–74. doi:10.1055/s-0039-1700546.
- 560 [15] Ducrocq G, Schulte PJ, Budaj A, Cornel JH, Held C, Himmelmann A, et al. Balancing the
561 risk of spontaneous ischemic and major bleeding events in acute coronary syndromes.
562 *American Heart Journal* 2017;186:91–9. doi:10.1016/j.ahj.2017.01.010.
- 563 [16] Prüller F, Milke OL, Bis L, Fruhwald F, Scherr D, Eller P, et al. Impaired aspirin-mediated
564 platelet function inhibition in resuscitated patients with acute myocardial infarction treated
565 with therapeutic hypothermia: a prospective, observational, non-randomized single-centre
566 study. *Ann Intensive Care* 2018;8:28. doi:10.1186/s13613-018-0366-x.
- 567 [17] Steblovnik K, Blinc A, Bozic-Mijovski M, Kranjec I, Melkic E, Noc M. Platelet reactivity in
568 comatose survivors of cardiac arrest undergoing percutaneous coronary intervention and
569 hypothermia. *EuroIntervention* 2015;10:1418–24. doi:10.4244/EIJY14M05_02.
- 570 [18] Qamar A, Bhatt DL. Current status of data on cangrelor. *Pharmacol Ther* 2016;159:102–9.
571 doi:10.1016/j.pharmthera.2016.01.004.
- 572 [19] Gori T, Polimeni A, Indolfi C, Räber L, Adriaenssens T, Münzel T. Predictors of stent
573 thrombosis and their implications for clinical practice. *Nat Rev Cardiol* 2019;16:243–56.
574 doi:10.1038/s41569-018-0118-5.
- 575



