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# 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

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ABSTRACT

*Aims:* To describe the characteristics and outcomes of patients receiving bailout glycoprotein IIb/IIIa inhibitors (GPI) for thrombotic complications of percutaneous coronary intervention (PCI) in a large, contemporary trial.
*Methods and results:* In the CHAMPION PHOENIX trial, the use of GPI was restricted to bailout for thrombotic complications. We describe the characteristics and outcomes of patients requiring bailout GPI compared to patients not receiving GPIs, with adjustment through propensity-score. A multivariable model was constructed to identify independent correlates associated with bailout GPI use.
A total of 380 out of 10,942 patients received GPI (3.5%); GPI patients were younger, more frequently male, more likely to present with ST segment elevation myocardial infarction and less frequently treated with cangrelor. At 48 h, GPI patients experienced higher rates of the primary composite outcome of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis (ST) (19.2% vs 4.8%; adjusted OR: 5.65(4.08, 7.82), $p < 0.0001$) and a higher rate of GUSTO severe or moderate bleeding (2.6% vs 0.4% adjusted OR: 4.90 (1.98, 12.18), $p = 0.0006$) compared with non GPI patients. Independent correlates of GPI use were STEMI, use of unfractionated heparin, drug-eluting stents and longer procedure duration.

*Abbreviations:* ACS, acute coronary syndrome; DCRI, Duke Clinical Research Institute; DSMB, Data Safety Monitoring Board; GPI, Glycoprotein IIb/IIIa Inhibitors; IDR, Ischemia-driven revascularization; MI, myocardial infarction; mITT, modified intent-to-treat; PCI, percutaneous coronary intervention; ST, stent thrombosis; STEMI, ST-elevation Myocardial Infarction.

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*Conclusions:* In a large contemporary trial, patients receiving bailout GPI for thrombotic complications of PCI experienced very high risks of both ischemic and bleeding complications, suggesting that prevention of periprocedural complications rather than bailout GPI may be preferable.
Clinical Trial Registration: http://www.clinicaltrials.gov identifier: NCT01156571.


## 1. Introduction

Reducing periprocedural ischemic/thrombotic events in patients undergoing percutaneous coronary intervention (PCI) is an important therapeutic goal in order to improve both short and long-term outcomes.

In the past decade, potent oral antiplatelet agents have emerged [1,2], leading to a decrease in adverse ischemic events after PCI, including stent thrombosis (ST) and myocardial infarction (MI) [3,4]. However, these drugs have limitations, including delayed onset of action due to the need for gastrointestinal absorption and in some cases the need for prodrug conversion to an active metabolite, and thus, may not be suitable for every situation. Conversely, intravenous glycoprotein IIb/IIIa inhibitors (GPI) are immediately effective and have previously shown efficacy in reducing the risk of periprocedural ischemic events [5–9]. However, concerns over high bleeding risk and cost have led to a steady decline in GPI use. Current European and US guidelines recommend that GPI be limited to bailout use for thrombotic procedural complications such as slow flow, no reflow, or angiographic evidence of a large thrombus. These recommendations (recommendation class IIa; level of evidence C) are based on expert consensus, given that only limited trial data are available regarding bailout use of GPI [10,11].

In the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PHOENIX trial [12,13] comparing cangrelor with clopidogrel in the setting of PCI, the use of GPI was limited to bailout therapy. In this contemporary PCI population, we sought to determine the patient characteristics, short term clinical outcomes, and independent correlates associated with bailout GPI use.

## 2. Methods

### 2.1. Study design

The design of CHAMPION PHOENIX and the primary trial results have been published previously [12,14]. In this double-blinded trial, 11,145 patients were randomized to either cangrelor bolus and infusion or a loading dose of clopidogrel (600 mg or 300 mg at the start or at the end of the procedure, both dose and timing at the discretion of the physician) in the setting of PCI for stable angina or acute coronary syndromes (ACS). A total of 10,942 patients received the study drug and underwent PCI, representing the prespecified modified intention to treat population (mITT) used for analysis. The study protocol prespecified the use of GPI for bailout only for procedural thrombotic complications that included intracoronary large thrombus, slow flow, no reflow, side branch compromise, dissection, or distal embolization. For the purposes of the present analysis, we defined all patients receiving GPI as bailout use, regardless of whether the case report form was marked as bailout use or not.

### 2.2. Study patients

Patients 18 years or older undergoing PCI either for stable angina or for ACS (myocardial infarction with or without ST-segment elevation) and who had not received pretreatment with P2Y12 inhibitors were eligible for enrolment. Written informed consent was required for trial participation. The main exclusion criteria were pregnancy or treatment with antithrombotic agents likely to interfere with the study drug such as $P2Y_{12}$ antagonists, abciximab within 7 days prior to randomization, eptifibatide, tirofiban, or fibrinolytic therapy within the prior 12 h.

### 2.3. Study treatments

Randomization was performed via an interactive voice response system (IVRS) in a double-dummy, double-blind manner, after angiography but prior to PCI. Randomization was stratified according to site, patient presentation (STEMI/NSTE-ACS/Stable angina), and planned clopidogrel loading dose (300 mg or 600 mg). Patients were then treated with either a cangrelor infusion (4 μg/kg/min after a 30 μg/kg bolus) for a minimum of 2 h or for the duration of the procedure length if the latter exceeded 2 h or a corresponding placebo. In addition, depending on whether the investigator chose to load clopidogrel at the start or the end of the procedure, they received a kit of capsules containing clopidogrel or a placebo. Periprocedural anticoagulant (unfractionated heparin, bivalirudin, low molecular weight heparin, or fondaparinux) use was at the investigator's discretion.

### 2.4. Outcomes

Ischemic outcomes included all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), or stent thrombosis (ST). They were combined in a primary composite ischemic outcome analyzed at 48 h post PCI. Safety outcomes included Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe and moderate bleeding at 48 h; bleeding was also categorized according to the Thrombolysis in Myocardial Infarction (TIMI) and Acute Catheterization and Urgent Intervention Triage (ACUITY) bleeding scales. Both ischemic and hemorrhagic outcomes were analyzed at 48 h, while ischemic outcomes were also assessed at 30 days. All ischemic outcomes were adjudicated by the Duke Clinical Research Institute (DCRI) Clinical Events Committee (CEC), while safety outcomes were site-reported and not centrally adjudicated [15]. Detailed outcome definitions have been previously published [12].

### 2.5. Statistical analyses

All the patients from the CHAMPION PHOENIX trial were included in this analysis. Baseline characteristics, ischemic and hemorrhagic outcomes were compared between patients who did or did not receive GPI. Continuous variables are summarized as medians and quartiles, or as means ± SD, as appropriate, and were compared using Student's *t*-test or Wilcoxon rank sum test accordingly. Categorical variables were presented as rate (%) and compared by the chi-square or Fisher's exact test as appropriate. In addition, a multivariable model including the above-mentioned variables was constructed to identify independent correlates associated with the need for bailout GPI. Regarding outcomes, given the protocol requirement that GPI use be restricted to bailout settings, substantial imbalance between groups in terms of clinical and procedural characteristics was anticipated. Accordingly, adjustment for such imbalance was performed through propensity-score adjustment of patients receiving versus patients not receiving GPI therapy using baseline demographic and procedural variables. (Propensity score based on treatment (cangrelor or clopidogrel), age ≥75 years/old, race (white/non-white), IVRS patient type according to clinical presentation (STEMI/NSTE-ACS/Stable angina), region (US/non-US), baseline cardiac marker status, diabetes mellitus, current smoking, hypertension, hyperlipidemia, stroke/TIA, prior MI, prior PCI, previous CABG, use of heparin or bivalirudin before or during the procedure, sex, DES/BMS, vessel disease (single/multi), weight, PCI duration).

All summaries and statistical analyses were performed using SAS® version 9.3 (Cary, NC).

## 3. Results

### 3.1. Baseline characteristics

Among 11,145 patients randomized in the trial, 10,942 patients received study drug and underwent PCI, thereby comprising the mITT population, which was prespecified as the population for the primary analysis of the trial. The frequency of bailout GPI use was 3.5% (380/10,942). Demographic characteristics and other baseline factors for the bailout GPI and no-GPI groups are presented in Table 1. As expected, the groups differed widely in terms of baseline characteristics with GPI patients being younger, more frequently male, and more frequently presenting with an ACS. Procedural characteristics presented in Table 1 also demonstrated differences between the two groups with patients receiving bailout GPI being more likely to receive a drug-eluting stent and to be less frequently treated with bivalirudin. Indications for GPI prescription are detailed in supplementary data.

### 3.2. Multivariable analysis

Multivariable analysis identified several independent correlates of the risk of bailout GPI use (Table 2). The main correlate was

**Table 1**
Baseline characteristics and procedural characteristics.

| | GPI ($N = 380$) | No GPI ($N = 10,562$) | $p$-Value |
|---|---|---|---|
| Age (mean ± SD, years) | 62.2 ± 11 | 64 ± 11 | 0.0015 |
| Male (%) | 294 (77.4) | 7597 (71.9) | 0.0201 |
| ACS presentation (%) | 301 (79.2) | 4283 (40.6) | <0.0001 |
| Diabetes (%) | 91 (24.1) | 2964 (28.1) | 0.0868 |
| Hypertension (%) | 244 (64.7) | 8462 (80.3) | <0.0001 |
| Current smoker (%) | 146 (39.2) | 2907 (28.2) | <0.0001 |
| Hyperlipidemia (%) | 183 (51.8) | 6518 (69.8) | <0.0001 |
| US region | 94 (24.7) | 4003 (37.9) | <0.0001 |
| Radial access | 95 (25.0) | 2760 (26.2) | 0.3259 |
| Multivessel disease (%) | 214 (56.5) | 5487 (52.0) | 0.0909 |
| ≥2 vessels treated (%) | 43 (11.4) | 1652 (15.8) | 0.0204 |
| Bivalirudin | 53 (13.9) | 2428 (23.0) | <0.0001 |
| Drug eluting stent | 241 (63.4) | 5840 (55.3) | 0.0017 |
| Total stents (mean ± SD) | 1.7 ± 0.9 | 1.5 ± 0.8 | <0.0001 |
| PCI duration (mean ± SD, min) | 37.7 ± 26.5 | 22.1 ± 18.9 | <0.0001 |

GPI: glycoprotein IIb/IIIa inhibitors, SD: standard deviation, ACS: acute coronary syndrome, US: United States.

ST-segment elevation MI (STEMI) presentation (adjusted OR (95% CI): 4.97 [3.76; 6.57], $p < 0.0001$). Other correlates were geographic region (with a higher rate of GPI use in the US) and procedural characteristics (use of heparin, use of drug-eluting stents, and longer PCI duration). Conversely stable angina was correlated with a lower rate of bailout use of GPI, as was hypertension, use of bivalirudin, and randomization to cangrelor.

### 3.3. Ischemic outcomes at 48 h

The risk for the primary composite efficacy outcome was much higher in patients requiring bailout use of GPI compared with patients who did not require GPI, even after adjustment for baseline and procedural differences: 19.2% in the group of patients receiving GPI vs 4.8%, OR (95% CI) 4.72 [3.61; 6.19] and after adjustment, OR (95% CI) 5.65 [4.08; 7.82]. Individual components of the primary outcome and additional outcomes are presented in Fig. 1. In brief, for each individual ischemic outcome at 48 h, rates were higher in the group requiring GPI, mainly driven by rate of ST (unadjusted rates: 10.3% vs 0.8%, OR (95% CI): 14.8 [9.95; 22.01] and adjusted OR (95% CI): 14.6 [8.86; 23.95], $p < 0.0001$) and MI (unadjusted rates 11.6% vs 4%, OR (95% CI): 3.18 [2.29; 4.42] and adjusted OR (95% CI): 6.15 [4.19; 9.03] $p < 0.0001$).

### 3.4. Bleeding outcomes at 48 h

The rate of bleeding was low overall, regardless of the definition used or of whether patients were treated with cangrelor or placebo. Rates of the safety outcome of GUSTO severe or moderate bleeding were higher in the GPI group (unadjusted: 2.6% vs 0.4% OR: 7.15 (3.55, 14.40), and after adjustment OR: 4.90 (1.98, 12.18), $p = 0.0006$), mostly driven by a higher risk of GUSTO moderate bleeding. The rates of TIMI major bleeding and transfusion were also higher in this group (Fig. 2).

**Table 2**
Correlates of GPI use.

| Variable | Adjusted OR (95% CI) | $p$ value |
|---|---|---|
| *Independent predictors of higher risk for bailout GPI* | | |
| STEMI | 4.97 (3.76, 6.57) | <0.0001 |
| Drug eluting stents | 2.02 (1.59, 2.55) | <0.0001 |
| US population | 1.74 (1.26, 2.39) | 0.0007 |
| Heparin | 1.45 (1.05, 2.00) | 0.0243 |
| PCI duration (per minute) | 1.03 (1.02, 1.03) | <0.0001 |
| *Independent predictors of lower risk for bailout GPI* | | |
| Stable angina | 0.30 (0.21, 0.41) | <0.0001 |
| Bivalirudin | 0.53 (0.35, 0.80) | 0.0028 |
| Hypertension | 0.63 (0.49, 0.80) | 0.0001 |
| Cangrelor | 0.64 (0.51, 0.80) | <0.0001 |

GPI: glycoprotein IIb/IIIa inhibitors, STEMI: ST elevation myocardial infarction, US: United States, PCI: percutaneous coronary intervention.

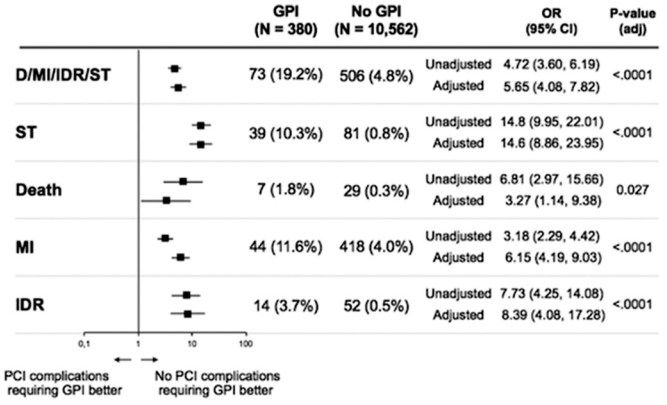


**Fig. 1.** Ischemic events at 48 h.

### 3.5. Outcomes at 30 days

At 30 days, results were consistent with those observed at 48 h: there was a higher rate of ischemic outcomes in the group of patients requiring bailout GPI both for the primary efficacy outcome (unadjusted rates: 21.6% vs 5.9%, OR (95% CI): 4.37 [3.38; 5.66] and adjusted OR (95% CI): 4.72 [3.47; 6.42] $p < 0.0001$) as well as the individual components including ST (10.8% vs 1.3%, OR (95% CI): 9.39 [6.51; 13.5] and adjusted OR (95% CI): 9.06 [5.74; 14.3] $p < 0.0001$) and MI (11.8% vs 4.3%, OR (95% CI): 3.0 [2.17; 4.15] and adjusted OR (95% CI): 5.45 [3.73; 7.96] $p < 0.0001$) (cf. Supplementary data).

## 4. Discussion

This analysis provides new data about bailout GPI use during PCI. The available evidence on the benefit/risk profile of GPI and the international guideline recommendations [10] reflect mostly the randomized controlled trials that investigated routine GPI use during PCI. To our knowledge, this is the largest single cohort reporting the characteristics and outcomes of patients requiring bailout GPI.

The first key finding pertains to the population: patients treated with bailout GPI were very different from the rest of the population. We speculate that the higher proportion of younger male patients may reflect the intent by investigators to target the subsets of patients

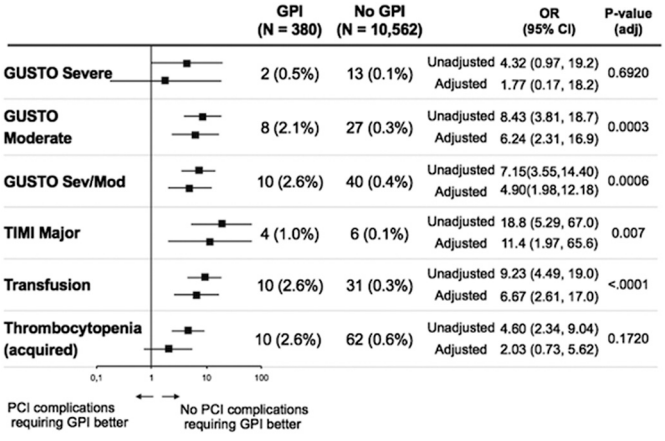


**Fig. 2.** Bleeding events at 48 h.

with lower risk of bleeding who would be more likely to tolerate GPI, as reported in earlier trials [6,8]. The higher frequency of GPI use in STEMI patients may be related to the associated high thrombotic burden and the increased risk for procedural thrombotic complications in these patients [16]. An additional rationale for the high rates of GPI use in STEMI is related to the inherent limitation of oral agents to provide a rapid antiplatelet effect [16].

A second observation pertains to the major differences in procedural characteristics between patients receiving or not receiving bailout GPI. In aggregate, patients receiving bailout GPI underwent more complex PCI procedures as evident by higher frequency of multivessel disease, a greater number of stents used during the PCI, as well as more frequent bifurcation target lesions and more frequent targeting of left main disease. Accordingly, procedural duration, a natural surrogate for procedural complexity, was also longer among patients receiving bailout GPI.

Bailout GPI use was less frequent among patients treated with bivalirudin. However, given differing utilization patterns of bivalirudin and GPI among US and non-US patients, residual confounding may also be at play [17]. Likewise, the association between drug eluting stent use and bailout GPI therapy may be in part confounded.

In the present analysis, bailout GPI was associated with higher rates of ischemic and bleeding events at 48 h reflecting the fact that the main trigger for use of bailout GPI is the occurrence of thrombotic complications, making it impossible to discern whether the poor outcomes were the result of the use of bailout GPI or reflective of the underlying complicated clinical course of the PCI procedure. Since no comparison with a control group was made, this analysis does not suggest GPI to be useless but rather that their use is unable to sufficiently lower the excess of risk carried by procedural PCI complications. Consistent with our observations, a higher rate of adverse events rate has been observed in patients receiving bailout GPI compared to planned GPI in the ONTIME-2 trial [18], suggesting that once a thrombotic complication has occurred, it may be difficult to modify the clinical outcome through a bailout strategy.

Thus, these data support the need to test alternative strategies to bailout use once thrombotic complications have occurred. The use of potent parenteral antiplatelet agents may be important in the STEMI setting whereas the onset of efficacy of oral agents may be delayed [19].

In the CHAMPION PHOENIX trial, cangrelor reduced ischemic events [12,13] and reduced the need for bailout GPI. A recent pooled analysis of the 3 CHAMPION trials showed that the efficacy of cangrelor in reducing periprocedural PCI complications was consistent regardless of the use of GPI [20,21,22]. This has important clinical implications: since most of the factors associated with the requirement for bailout GPI are non-modifiable, use of cangrelor is a strategy to reduce the need for bailout GPI. Indeed, in a meta-analysis of the three CHAMPION trials, cangrelor reduced the requirement for bailout/rescue GPIs compared with clopidogrel (2.6% vs 3.4%; $p < 0.001$), whereas the proportion of patients receiving routine GPIs was not affected by the use of cangrelor (9.8% vs 9.7%; $p = 0.96$). In addition, in another pooled analysis of CHAMPION trials, patients receiving cangrelor alone displayed an equivalent ischemic risk but a lower bleeding risk than those receiving clopidogrel and routine GPI. Cangrelor is a safe option for limiting GPI bailout but is also a safe option for replacing routine GPI use [23].

In TRITON TIMI 38 [24] and in PLATO [25], STEMI patients treated by prasugrel or ticagrelor tend to experience less use of GPI bail-out therapy compared with clopidogrel-treated patients. This difference was not statistically significant, perhaps due to low rates of bailout GPI, however, these data support the idea that potent $P2Y_{12}$ inhibition, by improving periprocedural safety and efficacy, may reduce the need for GPI, without worsening clinical outcome in case of needed bailout therapy.

## 5. Limitations

The present analysis has certain limitations. This is a post hoc secondary subset analyses from a large study designed for other scientific purposes, and therefore it has the limitations inherent to post hoc analyses. Second, the analysis of ischemic outcomes of patients treated by GPI is confounded, their use being per protocol triggered by the advent of an ischemic complication. However, reduction in bailout GPI use with cangrelor versus clopidogrel was present in the analysis of the randomized trial data. Then, in the propensity-score adjustment, information regarding thrombus burden might have been useful but was not available. Finally, the data presented are purely observational and no comparison with a control group was made in the setting of PCI complications.

## 6. Conclusion

In conclusion, in CHAMPION PHOENIX, patients experiencing periprocedural complications during PCI requiring bailout use of GPI were younger, more frequently male, and more likely to present with ST segment elevation myocardial infarction. They had higher rates of both ischemic and bleeding events. The need for bail-out GPI explains the association with higher ischemic rates, and the use of GPI explains the association with higher bleeding rates. These observations emphasize the need to prevent rather than have to treat the periprocedural complications of PCI.

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## Conflict of interest

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Steven Elkin is an employee of The Medicines Company.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.114.

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