Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: insights from the PRODIGY trial

Giuseppe Gargiulo MD, Francesco Costa MD, Sara Ariotti MD, Simone Biscaglia MD, Gianluca Campo MD, Giovanni Esposito MD, PhD, Sergio Leonardi MD, Pascal Vranckx MD, PhD, Stephan Windecker MD, Marco Valgimigli MD, PhD

PII: S0002-8703(16)00031-4
DOI: doi: 10.1016/j.ahj.2016.01.015
Reference: YMHJ 5109

To appear in: *American Heart Journal*

Received date: 12 October 2015
Accepted date: 20 January 2016

Please cite this article as: Gargiulo Giuseppe, Costa Francesco, Ariotti Sara, Biscaglia Simone, Campo Gianluca, Esposito Giovanni, Leonardi Sergio, Vranckx Pascal, Windecker Stephan, Valgimigli Marco, Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: insights from the PRODIGY trial, *American Heart Journal* (2016), doi: 10.1016/j.ahj.2016.01.015

Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6-month or 24-month DAPT duration: insights from the PRODIGY trial.

Giuseppe Gargiulo[1,2], MD, Francesco Costa[3,4], MD, Sara Ariotti[1], MD, Simone Biscaglia[5], MD, Gianluca Campo[5], MD, Giovanni Esposito[2], MD, PhD, Sergio Leonardi[6], MD, Pascal Vranckx[7], MD, PhD, Stephan Windecker[1], MD, Marco Valgimigli[1,3], MD, PhD.

RCT# NCT00611286

[1] Department of Cardiology, Bern University Hospital, Bern, Switzerland

[2] Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy

[3] Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

[4] Department of Clinical and Experimental Medicine, Policlinico 'G. Martino', University of Messina, Italy

[5] Cardiovascular Institute, Azienda Ospedaliero-Universitaria Sant'Anna, Ferrara, Italy

[6]Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy

[7]Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Hasselt, Belgium

Address correspondence to:

Marco Valgimigli, MD, PhD

Department of Cardiology, Bern University Hospital,

CH- 3010 Bern, Switzerland

Tel/Fax: +41 31 632 96 53/ +41 31 632 47 71

E-mail: marco.valgimigli@insel.ch

ABSTRACT

Background: Proton-pump inhibitors (PPIs) are frequently prescribed in combination with clopidogrel, but conflicting data exist as to whether PPIs diminish the efficacy of clopidogrel. We assessed the association between PPI use and clinical outcomes for patients treated with percutaneous coronary intervention (PCI) and dual antiplatelet therapy with clopidogrel plus aspirin.

Methods and Results: In the Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial, 1970 patients were randomized to 6- or 24-month DAPT at 30 days from index procedure. Among them, 738 patients (37.5%) received PPI (mainly lansoprazole; 90.1%) at the time of randomization. PPI users were older, most likely to be woman, had a lower creatinine clearance, presented more frequently with acute coronary syndrome (ACS) and had a higher CRUSADE bleeding score. After adjustment, the primary efficacy endpoint (composite of all-cause death, myocardial infarction and cerebrovascular accident) was similar between no PPI and PPI users (9.2% vs 11.5%; adj. HR: 1.051; 95% confidence interval [CI] 0.788-1.400; p=0.736). Bleeding rates did not differ between the two groups (BARC type 2, 3 or 5: adj. HR 0.996; 95% CI 0.672-1.474; p=0.980). Net clinical adverse events (NACE) were also similar in no PPI and PPI patients (12.9% vs 14.9%; adj. HR: 0.99; 95% CI 0.772-1.268; p=0.93). Results remained consistent at sensitivity analysis when focusing on the 548 patients who remained on PPI for the whole study duration.

Conclusions: The current findings suggest that the concomitant use of PPIs, when clinically indicated, in patients receiving clopidogrel is not associated with adverse clinical outcome.

Keywords: proton pump inhibitor, clopidogrel, DAPT, cardiovascular events, bleeding

INTRODUCTION

Dual antiplatelet therapy (DAPT) is the cornerstone of antithrombotic treatment in patients undergoing percutaneous coronary intervention (PCI), although its optimal duration still remains debated (1-3). Notably, these patients are frequently treated with a proton-pump inhibitor (PPI) in order to prevent gastrointestinal complications such as ulceration and bleeding or due to pre-existing gastric disease (4-7). However, clopidogrel is a pro-drug that requires metabolic transformation in the liver by cytochrome P-450 isoenzyme (mainly CYP2C19) to elicit its antiplatelet effect. PPIs are also metabolized by CYP enzymes, leading to a potential inhibition of CYP2C19 (mainly omeprazole and esomeprazole) translating into reduced metabolic activation of clopidogrel when taken together. Indeed, some pharmacodynamic studies demonstrated a reduction of clopidogrel-induced antiplatelet effect when a PPI, mainly omeprazole, was concomitantly administered (8-11). The Food and Drug Administration (FDA) and the European Medicine Agency (EMA) discourage the concomitant use of omeprazole and clopidogrel (12,13). The clinical impact of the combined administration has been studied but results have been discordant, with some studies reporting an increased risk of cardiovascular adverse events while others did not confirm this concern (5-7,11,14-23). Pooled analyses also provided inconclusive results, owing to the risk of misinterpretation related to poor quality observational studies, thus supporting the need for high quality studies (14,15).

Therefore, the purpose of the present sub-analysis of the PRODIGY randomized trial is to assess whether medical therapy with PPI compared to that without PPI may impact clinical outcomes in the setting of an all-comer population undergoing PCI and with a randomly allocated short (6-month) or prolonged (24-month) DAPT regimen, consisting of clopidogrel and aspirin.

METHODS

The design and main findings of the Prolonging Dual- Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) have been previously reported (1,24). Briefly, all-comer PCI patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES at three Italian sites were randomly allocated at 30 days to either 6 or 24 months of DAPT. Selection criteria were broad, reflecting routine clinical practice. Randomization to 6- or 24-month DAPT was stratified by center, ongoing ST-segment-elevation myocardial infarction (MI), the presence of diabetes mellitus, and need for intervening of at least one in-stent restenotic lesion. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committees of the three participating centers independently approved the protocol, and all participants gave written informed consent. For the present analysis, no extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

Treatment protocol

All patients received aspirin (75–100 mg orally indefinitely) and clopidogrel (75 mg/day) according to the randomization scheme as follows: for either 6 months in the short DAPT arm or 24 months in the prolonged DAPT arm irrespective of the previously implanted stent type or indication for PCI.

Follow-up

The randomized patients returned for study visits at 30 days, and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, asked for the antiplatelet therapy compliance and 12-lead electrocardiogram recordings were obtained.

PPI use

The decision to start the treatment with a PPI as well as the type of PPI to be used was left at the physician’s discretion, and was not randomly assigned or mandated by protocol. PPI use was identified both at study baseline and at each study follow-up visit, along with other concomitant

medication use. For the present analysis, patients were defined as PPI users if on treatment at 30-day follow-up visit, at the timepoint when the randomization to short versus long-term DAPT was performed. We performed sensitivity analyses to investigate the effect of PPI versus no PPI on clinical outcomes after excluding patients who had changed their initial status (no PPI or PPI) during the follow-up.

Study endpoints

The primary efficacy endpoint of the PRODIGY trial was the composite of death, MI, or cerebrovascular accident (CVA), while the key safety endpoint included Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. The net effect on the combined ischemic and bleeding complications was obtained by two net adverse clinical event (NACE) endpoints that were generated by combining the primary efficacy endpoint of death, MI, or CVA with either the primary safety endpoint of BARC type 2, 3, or 5 bleeding or with BARC type 3 or 5 events. Other endpoints included each component of the primary efficacy endpoint, cardiovascular death, stent thrombosis (ST) defined on the basis of the Academic Research Consortium criteria, and BARC type 3 or 5 bleeding. Other safety endpoints included bleeding events adjudicated according to the TIMI and GUSTO scales. All study endpoint definitions were previously reported.

All endpoints were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of the patients' treatment-group assignments. The time frame of interest for the primary endpoint was from 30 days (i.e. after the primary endpoint randomization) to 24 months.

Statistical analysis

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Continuous variables were compared between randomized groups using the Wilcoxon's rank sums test, whereas for binary variables the $\chi 2$ test was used.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for no PPI vs. PPI treated patients (i.e. values >1 indicated increased hazard in the PPI group) with a proportional hazards model. Cox-regression was used for multivariate analysis. Clinical and angiographic characteristics that were imbalanced at a nominal 5% significance level between the two groups treated or not treated with PPI were identified and included the final adjusted model; these included sex, age, creatinine clearance, clinical presentation and CRUSADE score. As sensitivity analyses, adjusted outcomes were also evaluated after excluding patients who had modified their PPI status (assumption of PPI in those with no PPI therapy at 30-day or interruption of PPI in those with PPI therapy at 30-day) during follow-up. Further sensitivity analyses included the assessment of adjusted outcomes with landmark analysis at 6-24 months and the analysis restricted to those patients treated with lansoprazole as PPI type (exclusion of other PPI types).

Interaction testing was performed to determine whether the effect of DAPT duration was consistent irrespective of PPI treatment on the primary and secondary endpoints of the study. This was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A two-sided probability value of <0.05 was considered significant. All analyses were based on the intention-to-treat principle, and were performed with SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Among 1,970 patients randomized to 6 versus 24-month DAPT at 30 days from the PCI, 738 (37.5%) patients were receiving a PPI. The majority of them were treated with lansoprazole (671 patients, 90.9%), while the others received pantoprazole (56 patients, 7.6%) and few patients received other PPI types (omeprazole, esomeprazole and rabeprazole, 1.5%).

Baseline characteristics of population with PPI and without PPI are summarized in **Table 1**, while **Table 2** describes their characteristics in the setting of the two randomized arms of DAPT regimens (24 versus 6-month). Compared with patients who did not receive PPI, those receiving PPI were older, more likely female, had a lower creatinine clearance, presented more frequently with acute coronary syndrome (ACS) and had a higher CRUSADE bleeding score (**Table 1** and **2**). The primary efficacy endpoint (composite of all-cause death, myocardial infarction and cerebrovascular accident) was similar between patients with PPI and without PPI use (9.2% vs 11.5%; adj. HR: 1.051; 95% confidence interval [CI] 0.788-1.400; p=0.736, **Figure 1**). Results were consistent across other secondary endpoints as reported in **Table 3**. Safety endpoints of bleeding did not differ between the two groups (BARC type 2, 3 or 5: adj. HR 0.996; 95% CI 0.672-1.474; p=0.980; BARC type 3 or 5: adj. HR 1.478; 95% CI 0.856-2.553; p=0.160; **Figure 1** and **Table 3**). Overall, major bleeding evaluated with different definitions were more frequent in PPI users compared with those without PPI (BARC 3 or 5: 3.7% vs 2.1%; TIMI major 1.5% vs 0.9%; GUSTO moderate or severe 3.7% vs 1.9%), however, after adjustment for confounding factors none of them remained significant (**Table 3**). The composite of efficacy and safety endpoints in the net clinical adverse events (NACE) was also similar in no PPI and PPI patients (12.9% vs 14.9%; adj. HR: 0.99; 95% CI 0.772-1.268; p=0.93; **Figure 1** and **Table 3**).

Finally, there was no signal for heterogeneity between PPI use and explored clinical endpoints with respect to randomized DAPT duration (**Figure 2, Supplementary Figure 1**; **Table 4** and **Supplementary Tables 1-3**).

At sensitivity analyses, PPI therapy during follow-up was taken into account (1-month: 738 PPI patients, 37%; 6-month: 685 PPI patients, 35%; 12-month: 690 PPI patients, 35%; 18-month: 709 PPI patients, 36%; 24-month: 734 PPI patients, 37%). A specific analysis of clinical outcomes was also performed in patients who remained consistently on a PPI throughout the follow-up period and excluding those who had started or interrupted PPI therapy. Results remained robust showing the absence of significant differences for ischemic and bleeding events (**Supplementary Table 4**). This was further confirmed by landmark analyses (**Supplementary Table 5**) and by restriction of analysis to lansoprazole as PPI (**Supplementary Table 6**).

DISCUSSION

The present post-hoc analysis from the PRODIGY randomized trial investigated the impact of concomitant PPI use on clinical outcomes in all-comer patients undergoing PCI and receiving DAPT with clopidogrel as thienopyridine component.

While at univariate analysis PPI use was associated with an increased risk of ischemic and bleeding events, after multivariate adjustment, PPI therapy was no longer related to different rates of ischemic events, bleeding or NACE at 2 years irrespective of the short or prolonged regimen of DAPT. The findings of our study are consistent with the results of the COGENT trial, showing thus no association of PPI use with increased risk of ischemic events.

Several studies assessing the inhibition of platelet aggregation suggested that PPIs may significantly reduce the antiplatelet effect of clopidogrel when the 2 drugs are coadministered (8-11). In particular, some PPIs (omeprazole and esomeprazole) highly inhibit CYP2C19 isoenzyme, while other PPIs are weak inhibitors (lansoprazole) or do not inhibit this isoenzyme (pantoprazole). However, the findings from pharmacodynamic studies may not necessarily translate into differences in clinical outcomes, and the design and quality of studies might be the major determinant of such contrasting evidence (14,15). Indeed, the majority of studies supporting an increased risk of cardiovascular ischemic events when using any type of PPI in patients on clopidogrel are

observational studies. Conversely, randomized trials and propensity-score matched studies did not support such concerns. Nonetheless, new evidence from a recent US analysis of more than 60,000 patients with gastroesophageal reflux disease (GERD) exposed to PPIs raised new questions by reporting a 1.2-fold increased risk of MI and a two-fold increased risk of cardiovascular mortality, irrespective of clopidogrel use (20).

PPI use was associated with an increased risk of MACE and MI, but not death and target vessel revascularization in the sub-group analysis of the BASKET trial (22). Similarly, the CAPRIE trial showed a higher rate of ischemic events among patients treated with PPIs and clopidogrel, while the most recent sub-analysis from the ADAPT-DES trial showed increased rate of MACE due to death and target vessel revascularization rather than MI or ST (17,23).

In contrast, the dedicated COGENT trial did not support these findings (16). This trial randomly assigned patients with an indication for DAPT to receive clopidogrel in combination with either omeprazole or placebo, in addition to aspirin. The composite of cardiovascular death, MI, revascularization or stroke did not differ, but gastrointestinal events were less frequent in the omeprazole group (16).

In the sub-group analyses of the PRINCIPLE and TRITON-TIMI 38 trials, a significant impact of PPI therapy on reducing the effect of clopidogrel on platelet aggregation was further substantiated. However, the pharmocodynamic changes did not translate into adverse clinical outcomes (11).

Our study is in line with and importantly adds to previous evidence indicating that the use of PPIs, largely consisting of lansoprazole, in conjunction with clopidogrel is safe. In addition, this observation held true in the 2 randomized groups of short versus long-term DAPT, indicating that PPI therapy does not increase ischemic events irrespective of whether clopidogrel is administered for short periods (i.e. 6 months), or prolonged times (i.e. 24 months). The incidence of ST was low and did not differ in patients with or without concomitant PPI use.

In the subgroup-analysis of the PLATO trial on PPI use, the association between PPI use and clinical adverse events in patients treated with clopidogrel was likely due to confounding (observed

also in those receiving ticagrelor and in those receiving non-PPI gastrointestinal drugs), with PPI use emerging as a marker for, rather than a cause of higher rates of cardiovascular adverse events (18). Interestingly, the role of confounding factors appeared to also be relevant in the present study as the PPI population showed an increased risk of both ischemic and bleeding events. However, following multivariate adjustment, differences in outcomes were no longer present.

PPI are often prescribed in patients with DAPT in order to reduce bleeding complications or due to specific clinical indication (ie gastric disease). Generally the PPI use is left to the discretion of clinicians and often a selection of patients is performed with those receiving PPI being at increased risk of ischemic and bleeding events. This explains at least in part the results of observational studies on PPI use and increased ischemic risk. In the present study, PPIs were prescribed to patients with a greater bleeding risk, as indicated by a more advanced age, more female patients and ACS, a worse renal function and a higher CRUSADE score. However, after adjustment for these confounding factors, the differences between PPI and no-PPI populations were not clinically relevant for the majority of clinical outcomes. Whereas the COGENT trial excluded patients with prior indication for PPI use or H2-receptor antagonists, patients at higher risk of GI bleeding, the results of the present study can be extended to an all-comer population of patients undergoing PCI and DAPT therapy.

Limitations

This is a post-hoc not randomized and not pre-specified analysis of the PRODIGY trial, and the prescription of a PPI was left to the physician's discretion.

Rates of overall but not specifically GI bleeding were evaluated and available for this analysis, so potential benefits of PPI on reducing GI bleeding events could not be analyzed.

Although multivariate adjustment was performed, it cannot be excluded that unknown/unmeasured factors may have impacted findings.

Data on PPI dosage were not prospectively collected, so it was not possible to make specific analysis on dose-dependent effects.

"In the PRODIGY, lansoprazole was by far the most frequently used PPI. Hence, it remains unclear whether our findings may be extrapolated to other PPIs such as omeprazole or esmoprazole". Genetic analysis to test the predisposition for reduced clopidogrel responsiveness was not available. Therefore, it cannot be excluded that PPIs may have a different impact on outcomes in this sub-group of patients.

CONCLUSION

Overall, PPI use was not associated with an increased risk of cardiovascular events in all-comer patients undergoing PCI and receiving DAPT. Our findings do not support the need to avoid concomitant use of PPIs and DAPT with aspirin plus clopidogrel, when clinically indicated.

REFERENCES

1. Valgimigli M, Campo G, Monti M et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015-26.
2. Valgimigli M, Costa F, Byrne R, Haude M, Baumbach A, Windecker S. Dual antiplatelet therapy duration after coronary stenting in clinical practice: results of an EAPCI survey. EuroIntervention 2015;11:68-74.
3. Navarese EP, Andreotti F, Schulze V et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ 2015;350:h1618.
4. Lai KC, Lam SK, Chu KM et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002;346:2033-8.
5. Gao QP, Sun Y, Sun YX, Wang LF, Fu L. Early use of omeprazole benefits patients with acute myocardial infarction. Journal of thrombosis and thrombolysis 2009;28:282-7.
6. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. Gastroenterology 2011;140:791-8.
7. Ng FH, Tunggal P, Chu WM et al. Esomeprazole compared with famotidine in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction. Am J Gastroenterol 2012;107:389-96.
8. Small DS, Farid NA, Payne CD et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. J Clin Pharmacol 2008;48:475-84.
9. Sibbing D, Morath T, Stegherr J et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thrombosis and haemostasis 2009;101:714-9.

10. Gilard M, Arnaud B, Cornily JC et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008;51:256-60.

11. O'Donoghue ML, Braunwald E, Antman EM et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009;374:989-97.

12. U.S. Food and Drug Administration. Public Health Advisory: Updated Safety Information about a drug interaction between Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC). 2010.

13. European Medicines Agency. Public statement on possible interaction between clopidogrel and proton pump inhibitors. 2010.

14. Melloni C, Washam JB, Jones WS et al. Conflicting results between randomized trials and observational studies on the impact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy: systematic review. Circulation Cardiovascular quality and outcomes 2015;8:47-55.

15. Cardoso RN, Benjo AM, DiNicolantonio JJ et al. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis. Open heart 2015;2:e000248.

16. Bhatt DL, Cryer BL, Contant CF et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909-17.

17. Dunn SP, Steinhubl SR, Bauer D, Charnigo RJ, Berger PB, Topol EJ. Impact of proton pump inhibitor therapy on the efficacy of clopidogrel in the CAPRIE and CREDO trials. J Am Heart Assoc 2013;2:e004564.

18. Goodman SG, Clare R, Pieper KS et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. Circulation 2012;125:978-86.

19. Harjai KJ, Shenoy C, Orshaw P, Usmani S, Boura J, Mehta RH. Clinical outcomes in patients with the concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention: an analysis from the Guthrie Health Off-Label Stent (GHOST) investigators. Circulation Cardiovasc Interv 2011;4:162-70.

20. Shah NH, LePendu P, Bauer-Mehren A et al. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. PloS one 2015;10:e0124653.

21. Aihara H, Sato A, Takeyasu N et al. Effect of individual proton pump inhibitors on cardiovascular events in patients treated with clopidogrel following coronary stenting: results from the Ibaraki Cardiac Assessment Study Registry. Catheter Cardiovasc Interv 2012;80:556-63.

22. Burkard T, Kaiser CA, Brunner-La Rocca H, Osswald S, Pfisterer ME, Jeger RV. Combined clopidogrel and proton pump inhibitor therapy is associated with higher cardiovascular event rates after percutaneous coronary intervention: a report from the BASKET trial. J Int Med 2012;271:257-63.

23. Weisz G, Smilowitz NR, Kirtane AJ et al. Proton Pump Inhibitors, Platelet Reactivity, and Cardiovascular Outcomes After Drug-Eluting Stents in Clopidogrel-Treated Patients: The ADAPT-DES Study. Circulation Cardiovasc Interv 2015;8.

24. Valgimigli M, Campo G, Percoco G et al. Randomized comparison of 6- versus 24-month clopidogrel therapy after balancing anti-intimal hyperplasia stent potency in all-comer patients undergoing percutaneous coronary intervention Design and rationale for the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY). Am Heart J 2010;160:804-11.

FIGURE LEGEND

Figure 1. **Survival free from ischemic and bleeding events according to PPI treatment.** Cox proportional model plot for the primary endpoint of death for all causes, myocardial infarction and cerebrovascular accident (A), bleeding defined as BARC class 3 or 5 (B) and net adverse clinical events (C) in patients treated or not treated with PPI. Dashed lines represent the unadjusted risk model. Solid lines represent the adjusted risk model.

Figure 2. Forest plots for clinical outcomes in short versus prolonged DAPT duration according to PPI treatment. PPI and no PPI subgroups are shown, with hazard ratios and 95% confidence intervals, for the primary endpoint of death for any cause, myocardial infarction (MI), or cerebrovascular accident (CVA), death for any cause, cardiovascular death, myocardial infarction, definite or probable stent thrombosis, BARC type 3 or 5 bleeding and net adverse clinical events (NACE) among patients randomly assigned to either the 6-month or the 24-month dual-antiplatelet therapy.

Figure 1.

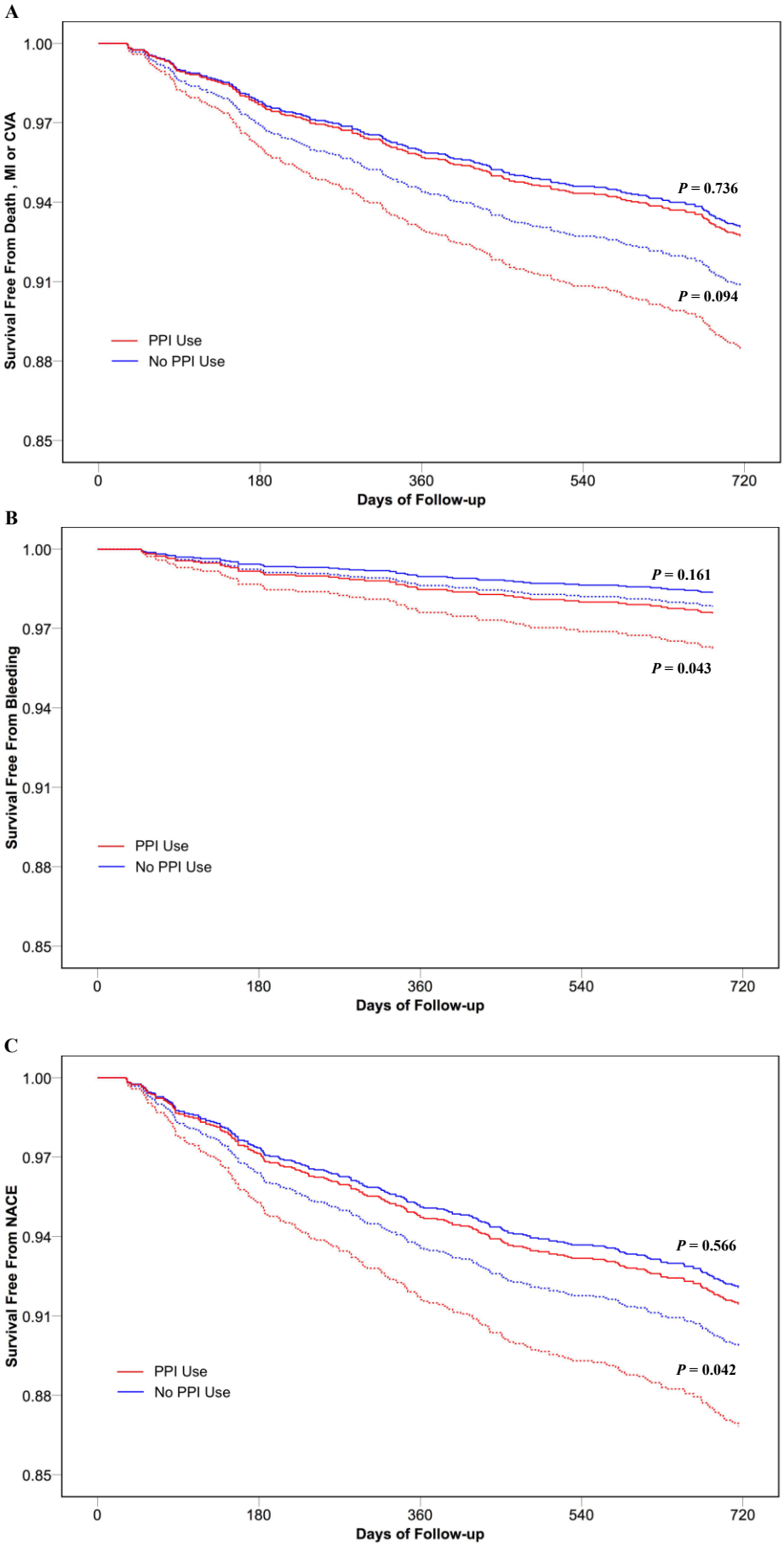

Figure 2.

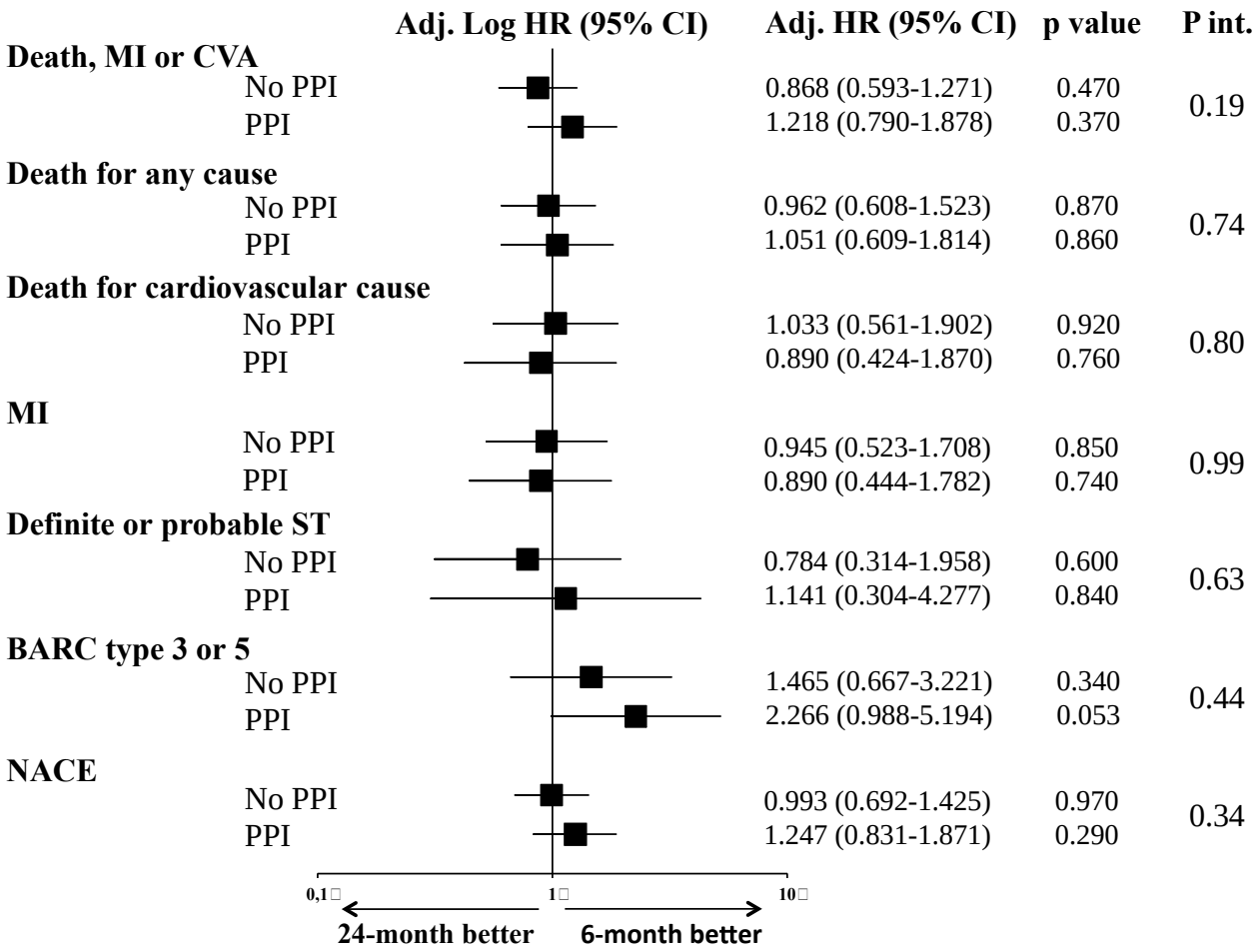

Table 1: Baseline characteristics in PPI versus no PPI treated patients

	No PPI (N=1232)	PPI (N=738)	p value
Age (yr)	68.1 (59.0-75.4)	71.2 (63.2-77.3)	<0.0001
Male sex	79.2% (976)	72.5% (535)	0.001
Body Mass Index (kg/m^2)	26.9 (24.7-29.4)	26.2 (24.2-29.3)	0.923
Diabetes	24.8% (305)	23.3% (172)	0.461
Insulin-dependent	5.7% (70)	6.0% (44)	
Hypertension	71.3% (879)	72.5% (535)	0.486
Hyperlipidemia	55.3% (681)	53.8% (397)	0.596
Current cigarette use	24.4% (301)	22.6% (167)	0.380
Creatinine Clearance (ml/min)	77.7 (58.3-99.2)	69.5 (53.3-91.0)	<0.0001
Prior myocardial infarction	26.1% (321)	27.0% (199)	0.520
Prior PCI	18.6% (229)	16.1% (119)	0.180
LVEF	55.0 (45-60)	50.0 (43-60)	0.080
Clinical presentation			
Stable angina pectoris	30.5% (376)	17.5% (129)	<0.0001
Acute Coronary Syndrome	69.5% (856)	82.5% (609)	
STEMI	30.2% (372)	37.4% (276)	0.001
NSTEMI	21.3% (262)	25.5% (188)	0.031
Unstable Angina	18.0% (222)	19.6% (145)	0.369
Multivessel Disease	70.5% (868)	69.2% (511)	0.569
No. of treated lesions	1 (1-2)	1 (1-2)	0.370
≥2 treated lesions	37.3% (459)	37.5% (277)	0.900
≥3 treated lesions	11.8% (145)	10.6% (78)	
Multivessel intervention	26.5% (327)	27.0% (199)	0.837
At least one complex lesion (Type B2 or C)*	67.0% (825)	65.2% (481)	0.416
Total ACC/AHA score†	3 (2-5)	3 (2-4)	0.600
CRUSADE score	24 (16-34)	27 (18-38)	<0.0001
Aspirin	100% (1232)	100% (738)	>0.999
Clopidogrel	98.8% (1230)	99.9% (737)	0.882
Statin	90.3% (1093)	90.9% (671)	0.627

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; CABG=Coronary Artery Bypass Graft; LVEF=Left Ventricle Ejection Fraction; NSTEMI=Non-ST-Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; PPI=Proton Pump Inhibitor; STEMI= ST-Elevation Myocardial Infarction.

* According to the ACC/AHA coronary lesion classification.

† Type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

Table 2: Baseline characteristics in PPI versus no PPI treated patients stratified for the randomly allocated DAPT duration

	24-Month Clopidogrel			6-Month Clopidogrel		
	No PPI (N=612)	**PPI (N=375)**	**p value**	**No PPI (N=620)**	**PPI (N=363)**	**p value**
Age (yr)	67.9 (58.9-74.5)	71.8 (63.8-77.7)	<0.0001	68.1 (59.2-76.6)	70.1 (61.7-76.9)	0.04
Male sex	80.6% (493)	72.3% (271)	0.003	77.9% (483)	72.7% (264)	0.070
Body Mass Index (kg/m^2)	27.0 (24.9-29.4)	26.0 (23.9-29.3)	0.450	26.8 (24.2-29.2)	26.4 (24.2-29.3)	0.200
Diabetes	24.7% (151)	24.8% (93)	0.900	24.9% (154)	21.8% (79)	0.290
Insulin-dependent	6.2% (38)	5.6% (21)		5.2% (32)	6.3% (23)	
Hypertension	71.4% (437)	75.7% (284)	0.140	71.3% (442)	69.1% (251)	0.410
Hyperlipidemia	56.5% (346)	55.2% (207)	0.680	54.0% (335)	52.3% (190)	0.640
Current cigarette use	23.9% (146)	20.3% (176)	0.200	25.3% (156)	25.1% (91)	0.450
Creatinine Clearance (ml/min)	77.7 (58.1-102.7)	68.9 (53.0-91.9)	0.001	77.8 (58.4-96.5)	70.7 (53.8-90.6)	0.002
Prior myocardial infarction	28.3% (173)	25.9% (97)	0.410	24.8% (154)	28.1% (102)	0.300
Prior PCI	20.9% (128)	16.3% (61)	0.070	17.7% (110)	16.5% (60)	0.490
LVEF	54.0 (43-60)	55.0 (45-60)	0.520	55.0 (45-60)	50.0 (40-60)	0.002
Clinical presentation						
Stable angina pectoris	31.2% (191)	17.1% (64)	<0.0001	29.8% (185)	17.9% (65)	<0.0001
Acute Coronary Syndrome	68.8% (421)	82.9% (311)		70.2% (435)	82.1% (298)	
STEMI	31.0% (190)	34.9% (131)	0.210	29.4% (182)	39.9% (145)	0.001
NSTEMI	21.1% (129)	25.9% (97)	0.080	21.5% (133)	25.1% (91)	0.190
Unstable Angina	16.7% (102)	22.1% (83)	0.03	19.4% (120)	17.1% (62)	0.370
Multivessel Disease	70.4% (431)	70.4% (264)	0.990	70.5% (437)	68.0% (247)	0.420
No. of treated lesions	1 (1-2)	1 (1-2)	0.320	1 (1-2)	1 (1-2)	0.780
≥2 treated lesions	37.4% (229)	36.3% (136)	0.720	37.1% (230)	38.8% (141)	0.590
≥3 treated lesions	11.4% (70)	10.1% (38)	0.520	12.1% (75)	11.0% (40)	0.610
Multivessel intervention	25.8% (158)	25.3% (95)	0.870	27.3% (169)	28.7% (104)	0.640
At least one complex lesion (Type B2 or C)*	67.3% (412)	61.3% (230)	0.060	66.6% (413)	69.1% (251)	0.410
Total ACC/AHA score†	3 (2-4)	3 (2-4)	0.600	3 (2-5)	3 (2-5)	0.840
CRUSADE score	24 (15-35)	28 (19-38)	<0.0001	24 (18-33)	27 (18-38)	0.004
Aspirin	100% (612)	100% (375)	>0.999	100% (620)	100% (365)	>0.999
Clopidogrel	99.8% (611)	99.7% (374)	0.726	99.8% (619)	100% (363)	0.444
Statin	89.2% (539)	90.4% (339)	0.560	91.3% (554)	91.5% (332)	0.920

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; CABG=Coronary Artery Bypass Graft; LVEF=Left Ventricle Ejection Fraction; NSTEMI=Non-ST-Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; PPI=Proton Pump Inhibitor; STEMI= ST-Elevation Myocardial Infarction.

* According to the ACC/AHA coronary lesion classification.
† Type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

Table 3: Clinical outcomes in PPI versus no PPI treated patients

	No PPI (N=1232)	PPI (N=738)	Unadjusted Hazard Ratio (95%CI)	p value	Adjusted Hazard Ratio (95%CI)	p value
Primary Efficacy Endpoint						
Death for any cause, MI or CVA	113 (9.2)	85 (11.5)	1.272 (0.960-1.685)	0.094	1.051 (0.788-1.400)	0.736
Secondary Efficacy Endpoints						
Death for any cause or MI	107 (8.7)	75 (10.2)	1.178 (0.877-1.582)	0.278	0.957 (0.708-1.293)	0.773
Death for any cause	77 (6.2)	53 (7.2)	1.150 (0.811-1.632)	0.433	0.918 (0.642-1.311)	0.636
Death for cardiovascular cause	44 (3.6)	29 (3.9)	1.101 (0.689-1.759)	0.688	0.865 (0.534-1.400)	0.554
MI	48 (3.9)	32 (4.3)	1.115 (0.713-1.744)	0.633	0.941 (0.597-1.485)	0.790
Definite or Probable ST	19 (1.5)	9 (1.2)	0.780 (0.353-1.723)	0.539	0.682 (0.306-1.523)	0.350
Definite, Probable or Possible ST	47 (3.8)	37 (5.0)	1.320 (0.858-2.030)	0.207	1.028 (0.662-1.597)	0.900
Safety Endpoints						
BARC classification						
Key safety endpoint (Type 2, 3 or 5)	64 (5.2)	43 (5.8)	1.127 (0.766-1.659)	0.545	0.996 (0.672-1.474)	0.980
Type 3 or 5	26 (2.1)	27 (3.7)	1.746 (1.019-2.992)	0.043	1.478 (0.856-2.553)	0.161
TIMI classification						
Minor	10 (0.8)	10 (1.4)	1.680 (0.699-4.036)	0.246	1.434 (0.589-3.492)	0.428
Major	11 (0.9)	11 (1.5)	1.679 (0.728-3.873)	0.224	1.465 (0.627-3.421)	0.378
Minor or major	21 (1.7)	21 (2.8)	1.684 (0.920-3.084)	0.091	1.453 (0.786-2.687)	0.234
GUSTO classification						
Moderate	13 (1.1)	14 (1.9)	1.803 (0.848-3.836)	0.126	1.449 (0.676-3.110)	0.341
Severe	12 (1.0)	13 (1.8)	1.820 (0.830-3.988)	0.135	1.626 (0.732-3.613)	0.232
Moderate or severe	24 (1.9)	27 (3.7)	1.893 (1.092-3.281)	0.023	1.582 (0.905-2.763)	0.107
Net Clinical Adverse Events (NACE)						
Death for any cause, MI, CVA or BARC 2, 3 or 5 Bleeding	159 (12.9)	110 (14.9)	1.172 (0.919-1.494)	0.202	0.989 (0.772-1.268)	0.933
Death for any cause, MI, CVA or BARC 3 or 5 Bleeding	125 (10.1)	97 (13.1)	1.317 (1.010-1.717)	0.042	1.083 (0.826-1.419)	0.566

Abbreviations: BARC=Bleeding Academic Research Consortium; CVA=Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI=Myocardial Infarction; PPI=Proton Pump Inhibitor; ST=Stent Thrombosis; TIMI=Thrombolysis in Myocardial Infarction.

Table 4: Adjusted clinical outcomes in in PPI versus no PPI treated patients stratified for the randomly allocated DAPT duration

	24-Month Clopidogrel				*6-Month Clopidogrel*				
	No PPI (N = 612)	**PPI (N =375)**	**Adjusted Hazard Ratio (95%CI)**	**P value**	**No PPI (N =620)**	**PPI (N = 363)**	**Adjusted Hazard Ratio (95%CI)**	**P value**	**P_{int}**
Primary Efficacy Endpoint									
Death for any cause, MI or CVA	52 (8.5)	48 (12.8)	1.375 (0.916-2.064)	0.125	61 (9.8)	38 (10.2)	0.852 (0.562-1.291)	0.449	0.19
Secondary Efficacy Endpoints									
Death for any cause or MI	48 (7.8)	40 (10.7)	1.218 (0.789-1.881)	0.372	59 (9.5)	35 (9.6)	0.824 (0.538 - 1.261)	0.372	0.33
Death for any cause	37 (6.0)	28 (7.5)	1.070 (0.645-1.777)	0.792	40 (6.5)	25 (6.9)	0.865 (0.519-1.441)	0.578	0.74
Death for cardiovascular cause	22 (3.6)	14 (3.7)	0.877 (0.437-1.757)	0.711	22 (3.5)	15 (4.1)	0.974 (0.494-1.923)	0.941	0.80
MI	23 (3.8)	16 (4.3)	0.980 (0.505-1.904)	0.953	25 (4.0)	16 (4.4)	0.923 (0.490-1.739)	0.803	0.99
Definite or Probable ST	8 (1.3)	5 (1.3)	0.718 (0.231-2.225)	0.566	11 (1.8)	4 (1.1)	0.652 (0.204-2.085)	0.471	0.63
Definite, Probable or Possible ST	19 (3.1)	19 (5.1)	1.431 (0.743-2.755)	0.283	28 (4.5)	18 (5.0)	0.868 (0.473-1.593)	0.647	0.34
Safety Endpoints									
BARC classification									
Key safety endpoint (Type 2, 3 or 5)	41 (6.7)	32 (8.5)	1.227 (0.762-1.977)	0.400	23 (3.7)	11 (3.0)	0.661 (0.321-1.362)	0.261	0.34
Type 3 or 5	15 (2.5)	19 (5.1)	1.881 (0.937-3.777)	0.076	11 (1.8)	8 (2.2)	1.048 (0.418-2.627)	0.920	0.44
TIMI classification									
Minor	7 (1.1)	4 (1.1)	0.741 (0.212-2.592)	0.639	3 (0.5)	6 (1.7)	3.572 (0.861-14.827)	0.080	0.15
Major	6 (1.0)	10 (2.7)	2.569 (0.905-7.290)	0.076	5 (0.8)	1 (0.3)	0.264 (0.031-2.265)	0.225	0.11
Minor or major	13 (2.1)	14 (3.7)	1.559 (0.717-3.391)	0.262	8 (1.3)	7 (1.9)	1.388 (0.479-3.739)	0.579	0.91
GUSTO classification									
Moderate	8 (1.3)	9 (2.4)	1.487 (0.562-3.934)	0.424	5 (0.8)	5 (1.4)	1.488 (0.424-5.222)	0.535	0.96

Severe	6 1.0)	10 (2.7)	2.569 (0.905-7.288)	0.076	6 (1.0)	3 (0.8)	0.705 (0.175-2.843)	0.623	0.26
Moderate or severe	13 (2.1)	19 (5.1)	2.079 (1.007-4.292)	0.048	11 (1.8)	8 (2.2)	1.050 (0.419-2.633)	0.917	0.31
Net Clinical Adverse Events (NACE)									
Death for any cause, MI, CVA or BARC 2, 3 or 5 Bleeding	87 (14.2)	65 (17.3)	1.140 (0.818-1.589)	0.440	72 (11.6)	45 (12.4)	0.875 (0.599-1.277)	0.489	0.60
Death for any cause, MI, CVA or BARC 3 or 5 Bleeding	61 (10.0)	55 (14.7)	1.329 (0.911-1.939)	0.141	64 (10.3)	42 (11.6)	0.928 (0.625-1.379)	0.712	0.34

Abbreviations: BARC=Bleeding Academic Research Consortium; CVA=Cerebrovascular Accident; GUSTO= Global Use of Strategies to Open Occluded Coronary Arteries; MI=Myocardial Infarction; PPI=Proton Pump Inhibitor; ST=Stent Thrombosis; TIMI=Thrombolysis in Myocardial Infarction.