Safety of prasugrel in real-world patients with ST-segment elevation myocardial infarction: 1-year results from a prospective observational study (Bleeding and Myocardial Infarction Study).

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Safety of Prasugrel in Real-World Patients with ST-Segment Elevation Myocardial Infarction: 1-year Results from a Prospective Observational Study (Bleeding and Myocardial Infarction Study)

Sécurité du Prasugrel chez des patients adressés pour un syndrome coronarien aigu avec sus-décalage du segment ST dans la "vraie vie": résultats d'une étude observationnelle prospective sur 1 an (Bleeding and Myocardial Infarction Study)

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ABSTRACT (WC = 250)

Background: Antiplatelet therapies, including prasugrel, are a cornerstone in the treatment of ST-elevation myocardial infarction (STEMI) but they are associated with a risk of bleeding. This risk has been evaluated in randomized trials but few data are known in real-world patients.

Methods: Consecutive patients with STEMI were recruited over one year. Follow-up was done at three months and at one year to evaluate the safety of prasugrel from hospital discharge to the anniversary date of the STEMI. The primary outcome was the occurrence of any major bleeding according to Bleeding Academic Research Consortium (BARC) 3 or 5 definitions or minor bleeding according to BARC 2 definition.

Results: 1083 patients were recruited. Compared to patients treated with aspirin + clopidogrel, patients treated with aspirin + prasugrel had less BARC 3 or 5 bleeding (9 patients, 1.8% versus 2 patients 0.4%, p=0.04) but more BARC 2 bleeding (20 patients, 4.0% versus 45 patients, 9.3%, p<0.001). Patients' baseline characteristics treated with prasugrel were different compared to those in patients treated with clopidogrel because they were carefully selected (younger patients, higher body max index, less history of stroke). This selection leads to a better control of bleeding risk. In the overall population, rates of in-hospital major bleeding and out-of-hospital major bleeding were 2.6% (n = 28) and 1.3% (n = 13) respectively.

Conclusion: Major bleeding, particularly out-of-hospital bleeding, in patients treated with prasugrel is low within one year after a STEMI. An accurate selection of patient candidates for prasugrel reduces the risk of bleeding.

RESUME

Introduction: Les traitements antiplaquettaires, dont le Prasugrel, sont un élément majeur dans le traitement du syndrome coronarien aigu avec sus-décalage du segment ST (SCA ST+) mais entraînent un sur-risque hémorragique. Ce risque a été évalué dans des essais cliniques randomisés mais il existe peu de données dans la « vraie vie ».

Méthodes : Les patients avec SCA ST+ ont été recrutés pendant un an et le suivi a été effectué, par téléphone, 3 mois et 1 an après le SCA ST+ afin d'évaluer la sécurité du Prasugrel, en particulier pendant la période post-hospitalière. Le critère d'évènement principal était la survenue d'un évènement hémorragique majeur défini selon la classification Bleeding Academic Research Consortium (BARC) 3 ou 5 ou d'un évènement hémorragique mineur défini selon la classification BARC 2.

Résultats : 1083 patients ont été recrutés. Les patients traités par Aspirine + Clopidogrel avaient moins de saignements BARC 3 ou 5 que les patients traités par Aspirine + Prasugrel (9 patients, 1,8% versus 2 patients, 0,4%, p = 0,04) mais ils avaient plus de saignements BARC 2 (20 patients, 4,0% versus 45 patients, 9,3%, p<0.001). Les caractéristiques des patients traités par Prasugrel étaient différentes des patients traités par Clopidogrel car la sélection était attentive : patients plus jeunes, indice de masse corporelle plus élevé, moins d'antécédent d'accident vasculaire cérébral. Cette sélection a permis un meilleur contrôle du risque hémorragique. Les pourcentages de saignement intra-hospitalier majeur et de saignement extra-hospitalier majeur étaient respectivement de 2,6% (n = 28) et 1,3% (n = 13).

Conclusion : Les saignements majeurs, en particulier extra-hospitaliers, sont peu fréquents chez les patients traités par Prasugrel dans l'année qui suit un SCA ST+. Une sélection attentive des patients pouvant bénéficier du Prasugrel permet une diminution de ce risque.

ABBREVATIONS LIST

ACS	Acute coronary syndrome
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass grafting
ENT	Ear, nose and throat
GRACE	Global Registry of Acute Coronary Events
MACE	Major adverse cardiac event
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
TRITON-TIMI	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI
VKA	Vitamin K antagonist

INTRODUCTION

Cardiovascular diseases, including acute myocardial infarction, are currently one of the leading causes of death in Western countries. Medical therapies focus on anticoagulation and platelet inhibition to reduce the risk of thrombotic events and improve ischemic outcomes of patients with ST-segment elevation myocardial infarction (STEMI). These, coupled with early use of cardiac catheterization and revascularization, reduce the rate of death and re-infarction but carry a bleeding risk. Indeed, bleeding is the most common non-cardiac complication of antithrombotic therapy in acute coronary syndromes (ACS) and has been associated with adverse outcomes, including myocardial infarction, stroke and death [1,2]. Thus, clinicians must balance antithrombotic treatment efficacy in preventing ischemic events with the need to minimize the risk of serious bleeding complications. Bleeding is even more frequent when percutaneous coronary intervention (PCI) is performed in the context of acute STEMI, when compared to bleeding complicating an elective procedure [3]. Several new antiplatelet therapies, including prasugrel, have been evaluated in randomized trials. They reduce the ischemic risk but are associated with an increased risk of major bleeding. In patients with STEMI undergoing PCI, prasugrel is more effective than clopidogrel for prevention of ischemic events, without excess in bleeding [4]. However, there are few data about the safety of new antiplatelet agents and bleeding risk within one year after a STEMI in real-world patients [5,6,7]. The Bleeding and Myocardial Infarction Study (Bleed-MI study) sought to evaluate the safety of prasugrel in real-world patients with STEMI, from hospital discharge to the anniversary date of the STEMI. Safety was assessed by analyzing the out-of-hospital bleeding.

METHODS

Study patients

Patients were included, from April 1, 2011 to March 31, 2012, if they had a STEMI and were hospitalized in any of the 9 primary percutaneous intervention centers in Brittany, France, within 24 hours after the onset of symptoms. There was no exclusion criterion. Data were recorded in the ORBI-registry. This registry was approved by the Commission Nationale Informatique et Liberté. All patients were informed of the aims of the study and could request to be excluded. The follow-up interviews were conducted by research nurses at three months and at one year by telephone. The follow-up questionnaire permitted key information about antiplatelet and anticoagulation therapies, medical treatment, and occurrence of bleeding or ischemic events. In case of bleeding or ischemic events, the hospitalization reports and all medical examination results (e.g., blood test, medical imaging, etc) were recovered so all data were centralized. Patients in whom follow-up data were lacking were considered lost to follow-up.

Definitions

The Bleeding Academic Research Consortium (BARC) [8] was used to define bleeding events occurring within one year after a STEMI. BARC 3 or 5 bleeding were considered major bleedings; BARC 2 bleeding were considered minor bleedings. BARC 1 bleedings were not collected because they do not require treatment by a healthcare professional. Thus, there collection would not have been exhaustive. Coronary artery bypass graft (CABG) – related bleeding (BARC 4 bleedings) were not analyzed. Bleeding rates were also defined according to Thrombolysis In Myocardial Infarction (TIMI) definitions [9].

Cardiovascular death was any death due to a new ACS, severe cardiac arrhythmia, refractory congestive heart failure, cardiogenic shock, stroke, sudden death or unwitnessed death. Acute myocardial infarction was defined in accordance with the universal definition of myocardial infarction proposed in 2012 [10]. Evaluation for stent thrombosis was performed according to the Academic Research Consortium criteria [11].

Study outcomes

The primary outcome was the occurrence of any minor or major bleeding between discharge and the end of the follow-up at one year. A "bleeding events" committee validated, classified, and located the site of each bleeding event, thanks to the phone interviews, the hospitalization reports and the medical examination results. Pre-specified secondary outcomes included in-hospital major bleeding and rates of premature stops (transitory or not) of any antithrombotic treatment after a bleeding complication. The rates of major adverse cardiac events (MACE), including cardiovascular death, nonfatal STEMI, nonfatal stroke, and stent thrombosis were calculated.

Statistical methods

Data description started with displaying the number of patients having hemorrhage or who were censored with no event at the date of point (12 months after myocardial infarction). Descriptive statistics included mean and standard deviation for normally distributed continuous variables, median and interquartile range otherwise and number and percentage for categorical variables. Comparisons according to dual antiplatelet regimen on discharge used chi-square or Fisher exact test for categorical variables and Student's *t* test or Wilcoxon test for continuous variables. For the main outcome, a survival analysis was used. Only one event per subject could occur in the analysis.

First, univariate (marginal) Wald test statistics using the Cox model were performed for each covariate. Then, multivariate modeling was completed with a Cox proportional hazards model that contained all covariates significantly associated in the univariate analyses at the P = 0.15 level. We used a hand-made stepwise backward elimination process: following the fit of the multivariable model, we used the P values from the Wald tests of the individual coefficients to identify covariates that might be deleted from the model. The linearity of the relationship between continuous covariates was not rejected except for hematocrit value when considering death; a cutoff at 37.4% was identified from martingale residuals analysis. In addition, the graphical and numerical methods derived from cumulative sums of martingale residuals over follow-up times or covariate values of Lin, Wei, and Ying [12] were used for checking the proportional hazard assumption. For all statistical analyses, SAS version 9.3 (SAS Institute, Cary, North Carolina) was used.

RESULTS

Study patients and in-hospital events

1083 consecutive patients with STEMI from nine centers in Brittany were recruited from April 2011 through March 2012. No patient requested to be excluded. Follow-up occurred from July 1, 2011 to March 31, 2013. The baseline characteristics of the patients are summarized in Table 1. Coronary angiography was performed in 1060 patients (97.9%), with radial access in 564 patients (53.2%) and angioplasty was performed in 974 patients (89.9%); 91.6% (n = 892) of stented patients received ≥1 stent, and 22.5% (n = 219) of stented patients had ≥1 drug- eluting stent. 2b3a inhibitors were used for 489 patients (45.2%).

In-hospital BARC 3 bleeding was observed in 28 patients (2.6%) and there was no in-hospital BARC 5 bleeding. Among these 28 patients, bleeding was attributed to a vascular access site in 7 patients (25%). In-hospital BARC 2 bleedings were not recorded. Switches from prasugrel to clopidogrel concerned 48 patients (4.4%), mainly for precaution of use.

Because of 51 in-hospital deaths (4.7%), 1032 patients were analyzed for follow-up. At discharge, 1021 patients (98.9%) were treated with aspirin, 513 patients (49.7%) were treated with clopidogrel, 484 patients (46.9%) were treated with prasugrel and 52 patients (5.0%) were treated with a vitamin K antagonist (VKA). Overall, 956 patients (92.6%) were treated with dual antiplatelet therapy alone and 32 patients (3.1%) were treated with a triple antithrombotic therapy (aspirin + clopidogrel + VKA or aspirin + prasugrel + VKA). Twenty-three patients (2.2%) were treated with only one antiplatelet agent (aspirin: 19 patients; clopidogrel: 3 patients; prasugrel: 1 patient). Data were missing for 23 patients (2.2%). A total of 26 patients (2.5%) were lost to follow-up at the end of the follow-up period (Figure 1).

Bleeding

An out-of-hospital major bleeding according to BARC 3 or 5 definitions occurred in 13 patients out of 1006 (1.3%) (Table 2). An out-of-hospital major bleeding according to TIMI definition occurred in 6 patients out of 1006 (0.6%). Total BARC 3 or 5 bleeding, including in-hospital bleeding, was observed in 41 patients (3.8%) and occurred during the first trimester in 33 patients (80.5% of major bleedings) (Figure 2). The most frequent out-of-hospital BARC 3 or 5 bleeding sites were gastrointestinal- (n = 6) and cerebral sites (n = 4). The most frequent out-of-hospital BARC 2 bleeding sites were ENT- (n = 26), cutaneous- (n = 14) and gastrointestinal sites (n = 12) (Table 3).

Patients treated with aspirin + prasugrel compared to patients treated with aspirin + clopidogrel had statistically significantly less BARC 3 or 5 bleeding (0.4% vs. 1.8%, respectively, p=0.04) but more BARC 2 bleeding (9.3% vs. 4.0%, respectively, p<0.001). Among the 988 patients treated with dual antiplatelet therapy, baseline characteristics of patients treated with prasugrel were different compared to those of patients treated with clopidogrel (Table 1). Patients treated with aspirin + prasugrel were more often male, younger, with a higher body max index, and with less history of arterial hypertension, stroke or transient ischemic attack. Patients treated with prasugrel were carefully selected: eight patients (1.7%) were aged ≥75 years among patients treated with prasugrel, while 193 patients (37.6%) were aged ≥75 years in the clopidogrel group. Thirteen patients (2.7%) weighed <60 kg among patients treated with prasugrel, whereas it concerned 107 patients (20.8%) in the clopidogrel group. Five patients (1.0%) had a history of stroke or transient ischemic attack among patients treated with prasugrel, whereas it concerned 19 patients (3.7%) in the clopidogrel group. In the Bleed-MI study, the rate of major out-of-hospital bleeding was low so it reduced the statistical power for detecting any clinical and biological predictors of bleeding events.

Antithrombotic agents

Among the 79 patients with out-of-hospital BARC 2, 3 or 5 bleeding, 25 patients were treated with aspirin + clopidogrel (5.2% of patients with this association), 45 with aspirin + prasugrel (9.5% of patients with this association), 2 with aspirin + VKA (14.3% of patients with this association), 4 with aspirin + clopidogrel + VKA (16% of patients with this association), 2 with aspirin + prasugrel + VKA (28.6% of patients with this association) and 1 with aspirin alone (5.3% of patients with aspirin alone). Thereby, 7.3% of patients (70/956)

treated with 2 antiplatelet agents underwent out-of-hospital bleeding, 18.7% of patients (6/32) treated with 3 antithrombotic agents underwent out-of-hospital bleeding. Moreover, 0.9% of patients (9/956) treated with dual antiplatelet therapy alone underwent a BARC 3 or 5 out-of-hospital bleed and 7.7% (4/52) of patients treated with a VKA underwent BARC 3 or 5 out-of-hospital bleeding. Anticoagulant agents therefore had an important role in the occurrence of major bleeding events.

Discontinuation of medication

Bleeding (BARC 2, 3 or 5) had led to temporary or definitive discontinuation of ≥ 1 antithrombotic agent in 27 out of 79 patients who had bleeding. Among these patients, prasugrel was replaced by clopidogrel for 5 patients. The discontinuation was definitive for 20 patients (74% of patients with discontinuation of treatment): aspirin in 2 patients, clopidogrel in 8, prasugrel in 8, VKA in 1, and prasugrel + VKA in 1 patient. The discontinuation was transient for 7 patients : aspirin in 3 patients, clopidogrel in 1, aspirin + clopidogrel in 1, and VKA in 2 patients. The mean delay of antithrombotic agent discontinuation was 6.5 months (± 4.5). Antithrombotic agents were interrupted before month 6 in 13 patients (48.1%), after month 6 in 14 patients (51.9%), and beyond month 9 in 11 patients (40.7%).

The most frequent bleeding sites leading to treatment discontinuation were gastrointestinal (25.9%), ENT (25.9%) and cutaneous (25.9%). Interestingly, bleeding that led to discontinuation of medications was not major in most of cases. In fact, 74.1% of those bleeds were BARC 2, 14.8% BARC 3a, 3.7% BARC 3b, and 7.4% were BARC 3c. No ischemic event was observed after discontinuation of antithrombotic medications. There was no relation found between bleeding occurrence and increased risk of ischemic event.

Predictive factors of death

Forty-four patients (4.4%) died from any cause during follow-up. From multivariable analysis, the factors independently associated with death included age (HR, 2.2; 95% CI, 1.6–3.0; P < 0.001), signs of congestive heart failure on presentation (HR, 4.1; 95% CI, 2.1–8.1; P < 0.001) and baseline hematocrit ≤ 37.4% (HR, 0.3; 95% CI, 0.2–0.6; P < 0.001). Although any BARC 3 or 5 bleedings predicted death in univariate analysis, they did not remain independent predictors of death after adjustment with other covariates. It was the same for sex, weight, body mass index, prior hypertension, prior coronary heart disease, prior chronic renal disease, baseline creatinine, and hospitalization duration.

Out-of hospital ischemic events

The rate of out-of-hospital MACE among patients with BARC 2, 3 or 5 bleeding was 7.6% (6 patients). There was no statistically significant difference compared to the entire population. Among all patients, the rate of out-of-hospital MACE was 6.1% (61 patients): death from cardiovascular causes occurred in 24 patients (2.4%), nonfatal MI in 10 (1.0%), nonfatal non-STEMI in 7 (0.7%), nonfatal stroke in 5 (0.5%), fatal stent thrombosis in 8 (0.8%), and nonfatal stent thrombosis in 7 patients (0.7%). The rate of stent thrombosis was 1.5%: 5 patients had a definite-, 5 patients had a probable-, and 5 patients had a possible stent thrombosis.

DISCUSSION

The Bleed-MI study allowed the evaluation of safety of prasugrel in non-selected STEMI patients in a real-world setting, according to the bleeding risk. This knowledge is crucial for the clinician who should choose the best antithrombotic treatment and its optimal duration according to the ischemic and bleeding risks. The final decision concerning an

individual patient must be made by the responsible physician taking into account the balance benefit/risk as recalled in the last European Society of Cardiology Guidelines for the management of STEMI [3].

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI 38) [13], patients aged ≥75 years showed no net benefit from prasugrel and there were no statistically significant higher rates of non-CABG-related TIMI major bleeding in the prasugrel group versus the clopidogrel group (4.3% vs. 3.3%, p=0.10). In the Bleed-MI study, patients treated with prasugrel compared to patients treated with clopidogrel had more BARC 2 bleeding but less BARC 3 or 5 bleeding. This low risk of major bleeding in prasugrel-treated patients in this real-life registry, despite frequent use, is reassuring and can be explained by the selection of patient candidates for prasugrel (lower bleeding risk patients). It means that the contraindications and the precautions for use of prasugrel are relevant. Moreover, it means that physicians are using the drug appropriately in appropriate candidates. Nevertheless, 33 patients (6.81% of patients treated with prasugrel) with contraindications or precautions for use of prasugrel received prasugrel in the study: 5 patients with history of stroke or TIA, 8 patients aged ≥75 years and 13 patients weighing < 60 kg, 7 patients with concomitant use of VKA.

Unlike many studies, we included non-selected patients, which make our results useful in real-world practice. Most studies include selected patients (patients undergoing PCI for STEMI for example). In the Bleed-MI study, coronary angiography was not performed for 22 patients (2%) and no angioplasty was performed for 109 patients (10.1%). These patients are rarely studied in randomized trials. Moreover, we focused on out-of-hospital events: the in-hospital bleeding, often related to procedural bleeding complications (PCI or CABG) should

be differentiated from out-of-hospital bleeding. The rate of out-of-hospital major bleeding within 1 year after a STEMI was low at 1.3% according to the BARC definition and 0.6% according to the TIMI definition. The rate of major out-of-hospital bleeding is particularly low in patients treated with prasugrel due to accurate selection of patients. The chronology of major bleeding is important due to its impact on the duration of antithrombotic treatment association in high bleeding risk patients. Bleeding can lead to a transitory or permanent discontinuation of one or more antithrombotic treatments, with the risk of stent thrombosis in stented patients and the risk of ischemic complications in all patients. In total, 68.3% of major bleedings occurred during the initial hospitalization. In a study published by Collet [14] in 2004, 5.4% patients admitted for a suspected ACS had recently withdrawn antiplatelet agents, which was found to be an independent predictor of mortality and bleeding at 30 days. In the Bleed-MI study, out-of-hospital bleeding (BARC 2, 3 or 5) led to early discontinuation of any thrombotic agent (before 6 months) in only 13 patients (16.5% of out-of-hospital bleedings). Moreover, there was no ischemic event among the 27 patients who discontinued their treatment. Bleeding (including minor bleeding) must not be underestimated and should be systematically sought during the medical follow-up of patients after ACS since it would promote treatment compliance.

The reported rates of major bleedings at 9-12 months' follow-up after ACS vary from 2 to 6% [15,16,17,18]. In the Bleed-MI study, in-hospital and out-of-hospital major bleeding occurred in 3.8% according to BARC definition and 1.5% according to TIMI definition. In TRITON-TIMI 38 [13], the rate of non-CABG-related TIMI major bleeding at 15 months in the entire population was 2%. Considering only patients undergoing PCI for STEMI [4], the risk of non-CABG major bleeding was lower (1.1%), which is close to our rate of 1.5%. In the

PLATO study [15], the rate of non-CABG-related TIMI major bleedings at 12 months among patients with a STEMI was 2.2%. Considering the localization of bleedings in our study, the most frequent out-of-hospital major bleeding sites are gastrointestinal, but the most frequent out-of-hospital minor bleeding sites are ENT and cutaneous sites and the most severe out-of-hospital bleeding sites are cerebral. In the Global Registry of Acute Coronary Events (GRACE) study [19], the most common life-threatening in-hospital bleeding complications were also gastrointestinal.

LIMITATIONS

As in any registry, this observational study has some limitations. For instance, 26 patients (2.5%) were lost to follow-up. The follow-up was made by telephone contact at 3 months and at 1 year but data collection was done by qualified hospital staff with directed questionnaires, which limits the loss of data. Moreover, BARC 1 bleedings were not collected because there collection would not have been exhaustive, due to the declaratory nature of data collection. Premature treatment cessation due to BARC 1 bleedings could then not have been analyzed.

No patient was treated with Ticagrelor because this treatment was not yet available in Brittany during the study.

According to an analysis from the TRITON-TIMI 38 study [20], independent predictors of non-CABG-related serious bleeding throughout 15 months were female sex, use of glycoprotein IIb/IIIa inhibitor, duration of intervention, age, assignment to prasugrel versus clopidogrel, STEMI, femoral access, creatinine clearance, hypercholesterolemia, and hypertension. In the Bleed-MI study, the low rate of major out-of-hospital bleedings reduced

the statistical power for detecting clinical and biological predictors of bleeding events. Any usual predictors of bleeding events could not be found and no statistical association between the occurrence of major bleeding and mortality was demonstrated.

CONCLUSION

Major bleeding rate, in patients treated with prasugrel after STEMI within one year after a STEMI is low when patients are carefully selected. The question remains of extending the prescription of new antiplatelet agents to a broader population of patients but with the risk of modifying the benefit-risk balance that we have documented in real world selected patients.

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TABLES AND FIGURES LEGENDS

TABLES

Table 1. Baseline Characteristics of the Patients

	Population (n=1083)	Aspirin + Clopidogrel (n = 505)	Aspirin + Prasugrel (n = 483)	p
Median age – yr	62.7±14.0	67.3±14.2	55.9±10.2	<.0001
Female sex - n (%)	282 (26.0)	171 (33.9)	67 (13.9)	<.0001
Median body weight - kg	75.5 ± 15.0	71.2±14.7	80.7±13.4	<.0001
BMI - kg/m²	26.3 ± 4.3	25.4±4.3	27.2±4.0	<.0001
Cardiovascular risk factor - n (%)				
Habitual smoker	439 (40.5)	159 (31.7)	254 (52.6)	<.0001
Arterial hypertension	460 (42.5)	252 (49.9)	150 (31.1)	<.0001
Diabetes mellitus	147 (13.6)	72 (14.3)	59 (12.2)	0.3441
Other medical history – n (%)				
Stroke/AIT	34 (3.1)	20 (4.0)	5 (1.0)	0.0034
Chronic renal disease	23 (2.1)	15 (3.0)	5 (1.0)	0.0309
Gastroduodenal ulcer	34 (3.1)	11 (2.2)	7 (1.4)	0.3918
Initial use of 2b3a inhibitors	489 (45.2)	233 (46.1)	233 (48.2)	0.51
Bleeding- n (%)				
Total		23 (4.6)	43 (8.9)	0.0110
BARC 2		15 (3.0)	42 (8.7)	0.0003
BARC 3		6 (1.2)	1 (0.2)	0.1246

BARC 5	2 (0.4)	0 (0)	0.4998
BARC 3 + 5	8 (1.6)	1 (0.2)	0.0389

BMI indicates body mass index; CABG, coronary artery bypass grafting ; PCI, percutaneous coronary intervention; TIA, Transient Ischemic Attack; BARC, Bleeding Academic Research Consortium.

Table 2. Chronology of Bleeding: In-hospital and Out-of-hospital Bleeding

	In-hospital bleeding (n=1083)	Out-of-hospital bleeding (n=1006)
BARC definition- n (%)		
BARC 2 bleeding	Not collected	66 (6.6)
BARC 3 bleeding	28 (2.6)	11 (1.1)
BARC 3a	17 (1.6)	6 (0.6)
BARC 3b	9 (0.8)	3 (0.3)
BARC 3c	2 (0.2)	2 (0.2)
BARC 5 bleeding	0 (0)	2 (0.2)
BARC 5a	0 (0)	2 (0.2)
BARC 5b	0 (0)	0 (0)
BARC 3 or 5 bleeding	28 (2.6)	13 (1.3)
TIMI definition- n (%)		
TIMI major bleeding	10 (0.9)	6 (0.6)
TIMI major or minor bleeding	22 (2.0)	13 (1.3)

BARC indicates Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction.

Table 3. Localization of out-of-hospital bleeding and vascular access

	BARC- n			Radial access- n (%)
	BARC 2	BARC 3	BARC 5	
Cutaneous	14	1	0	5 (33)
Gastrointestinal	12	6	0	13 (72)
Cerebral bleeding	0	2	2	0 (0)
ENT	26	0	0	15 (57)
Respiratory tract bleeding	5	0	0	2 (40)
Urinary tract bleeding	5	0	0	4 (80)
Others	4	2	0	3 (50)
Total	66	11	2	42 (53)

FIGURES

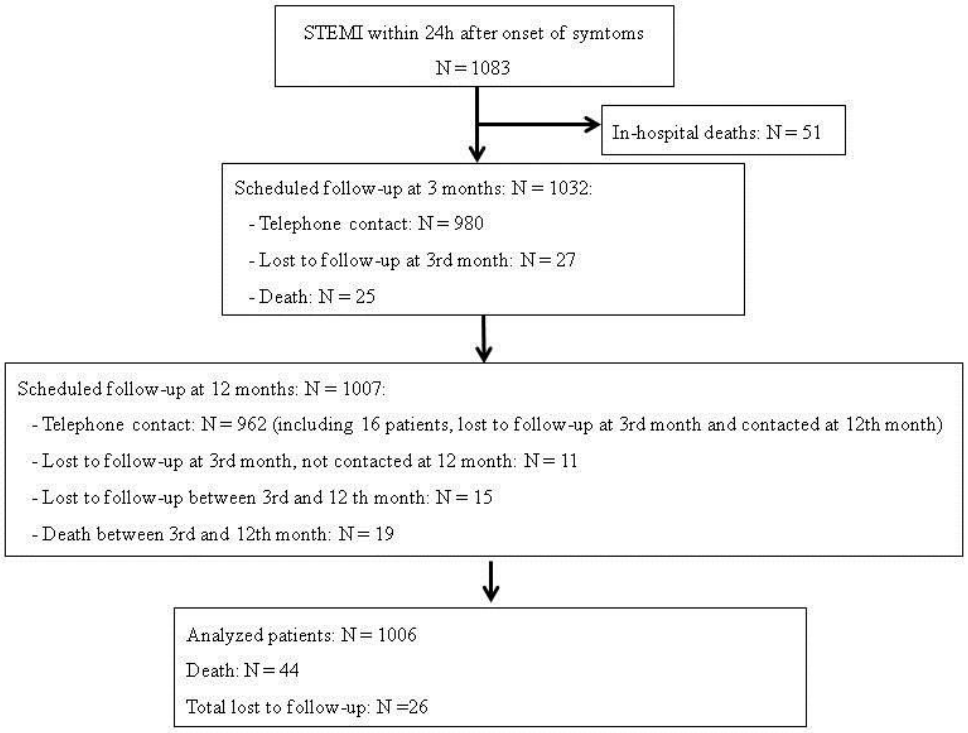

Figure 1. Flow-Chart. STEMI indicates ST-segment elevation myocardial infarction.

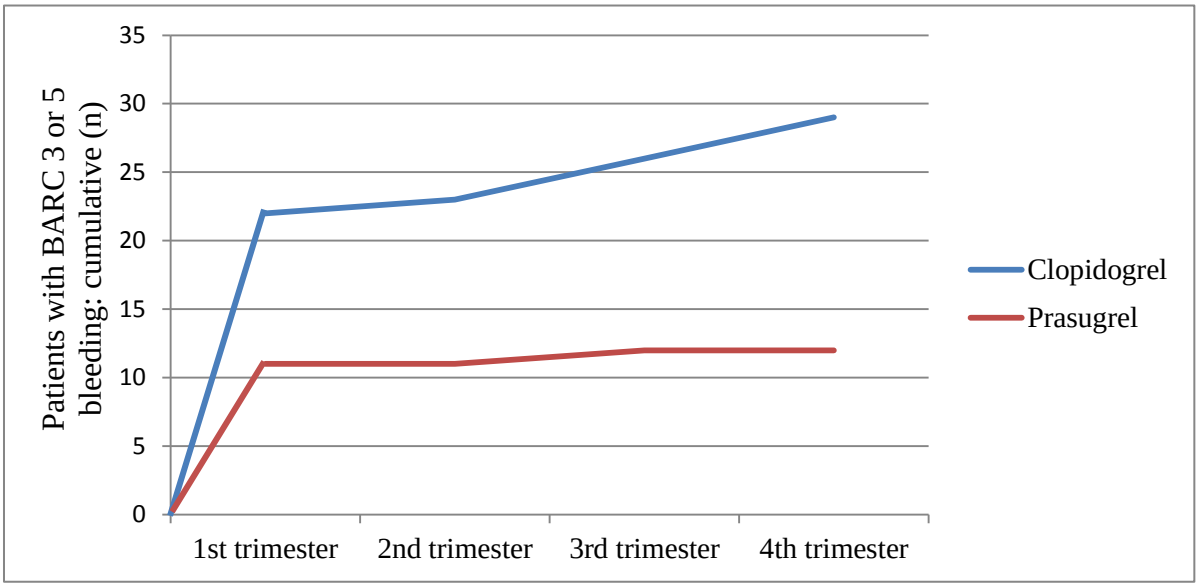

Figure 2. Patients with BARC 3 or 5 Bleeding during the Follow-up Period. BARC indicates Bleeding Academic Research Consortium.