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Safety of Prasugrel Loading Doses in Patients Pre-Loaded With Clopidogrel in the Setting of Primary Percutaneous Coronary Intervention

Results of a Nonrandomized Observational Study

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ABSTRACT

OBJECTIVES The aim of this study was to assess the safety of the concurrent administration of a clopidogrel and prasugrel loading dose in patients undergoing primary percutaneous coronary intervention.

BACKGROUND Prasugrel is one of the preferred $P2Y_{12}$ platelet receptor antagonists for ST-segment elevation myocardial infarction patients. The use of prasugrel was evaluated clinically in clopidogrel-naive patients.

METHODS Between September 2009 and October 2012, a total of 2,023 STEMI patients were enrolled in the COMFORTABLE (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI]) and the SPUM-ACS (Inflammation and Acute Coronary Syndromes) studies. Patients receiving a prasugrel loading dose were divided into 2 groups: 1) clopidogrel and a subsequent prasugrel loading dose; and 2) a prasugrel loading dose. The primary safety endpoint was Bleeding Academic Research Consortium types 3 to 5 bleeding in hospital at 30 days.

RESULTS Of 2,023 patients undergoing primary percutaneous coronary intervention, 427 (21.1%) received clopidogrel and a subsequent prasugrel loading dose, 447 (22.1%) received a prasugrel loading dose alone, and the remaining received clopidogrel only. At 30 days, the primary safety endpoint was observed in 1.9% of those receiving clopidogrel and a subsequent prasugrel loading dose and 3.4% of those receiving a prasugrel loading dose alone (adjusted hazard ratio [HR]: 0.57; 95% confidence interval [CI]: 0.25 to 1.30, $p = 0.18$). The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) bleeding score tended to be higher in prasugrel-treated patients ($p = 0.076$). The primary safety endpoint results, however, remained unchanged after adjustment for these differences (clopidogrel and a subsequent prasugrel loading dose vs. prasugrel only; HR: 0.54 [95% CI: 0.23 to 1.27], $p = 0.16$). No differences in the composite of cardiac death, myocardial infarction, or stroke were observed at 30 days (adjusted HR: 0.66, 95% CI: 0.27 to 1.62, $p = 0.36$).

CONCLUSIONS This observational, nonrandomized study of ST-segment elevation myocardial infarction patients suggests that the administration of a loading dose of prasugrel in patients pre-treated with a loading dose of clopidogrel is not associated with an excess of major bleeding events. (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI] [COMFORTABLE]; NCT00962416; and Inflammation and Acute Coronary Syndromes [SPUM-ACS]; NCT01000701). (J Am Coll Cardiol Intv 2015;8:1064–74) © 2015 by the American College of Cardiology Foundation.

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Rapid, potent, and consistent inhibition of platelet aggregation is a cornerstone in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary coronary intervention (PCI) to complement optimal epicardial and myocardial reperfusion while protecting against recurrent ischemic events (1). The administration of a clopidogrel loading dose before primary PCI has been shown to reduce ischemic events, with a 600-mg loading dose emerging as the preferred regimen (2,3). Compared with clopidogrel, prasugrel provides a more rapid onset and more potent and consistent inhibition of platelet aggregation (4,5). In STEMI patients undergoing PCI, prasugrel has been shown to be more effective than clopidogrel by reducing the risk of cardiovascular mortality, myocardial infarction, and stroke as well as stent thrombosis (6). Of note, improved efficacy in STEMI patients was not associated with an increased risk of bleeding throughout 15 months of follow-up. Recent guidelines for the management of STEMI patients recommend prasugrel over clopidogrel in patients undergoing primary PCI, without commenting on the use of prasugrel in clopidogrel pre-treated patients (7,8). Clopidogrel, however, is frequently administered upstream, even in STEMI patients. The administration of a prasugrel loading dose in patients already exposed to clopidogrel has raised concerns about bleeding and potential drug interactions, thereby potentially offsetting beneficial effects in terms of efficacy. We therefore assessed the safety and efficacy of 2 loading regimens consisting of clopidogrel and a subsequent prasugrel loading dose and a prasugrel loading dose alone using pre-specified endpoint definitions for safety and efficacy with assessment of adverse events by an independent adjudication committee in a large, contemporary population of STEMI patients undergoing primary PCI. Because no effect of a concomitant loading dose of clopidogrel and prasugrel is expected during the maintenance period of the therapy, the endpoints were assessed at hospital discharge and at 30 days.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BARC = Bleeding Academic Research Consortium

CI = confidence interval

HR = hazard ratio

IPTW = inverse probability of treatment weighted

PCI = percutaneous coronary intervention

PRU = platelet reactivity unit

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

METHODS

PATIENT POPULATION. Patients with STEMI were considered when participating in the COMFORTABLE (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI]) trial or in the SPUM-ACS (Inflammation and Acute Coronary Syndromes) trial and receiving either a prasugrel loading dose alone or a clopidogrel loading dose and a subsequent prasugrel loading dose. The design of the COMFORTABLE trial has been reported elsewhere (9,10). Briefly, this was a multicenter, randomized, assessor-blinded superiority trial comparing a novel biodegradable polymer-based biolimus-eluting stent with a bare metal stent in STEMI patients undergoing primary PCI. Consecutive patients 18 years of age or

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older with acute ST-segment elevation of at least 1 mm in ≥2 contiguous leads, true posterior myocardial infarction, or new left bundle branch block were eligible for randomization in the presence of at least 1 culprit lesion in the infarct vessel. Exclusion criteria were the presence of mechanical complications of acute myocardial infarction, known allergy to any study medication, use of vitamin K antagonists, planned surgery unless dual antiplatelet therapy could be maintained throughout the perisurgical period, history of bleeding diathesis or known coagulopathy, pregnancy, participation in another trial before reaching the primary endpoint, inability to provide informed consent, and noncardiac comorbid conditions with a life expectancy <1 year.

The SPUM-ACS cohort study is a multicenter, observational cohort study of patients presenting with acute coronary syndrome (ACS) conducted at 4 Swiss university hospitals (in Bern, Geneva, Lausanne, and Zurich). Inclusion criteria were the presence of an ACS and age older than 18 years. Exclusion criteria comprised severe physical disability, inability to comprehend study, and life expectancy <1 year. For the purpose of the present analysis, all STEMI patients included in the SPUM-ACS with the same qualifying diagnostic criteria as in the COMFORTABLE trial were selected. Both studies complied with the Declaration of Helsinki and were approved by local institutional ethics committees. All patients provided written, informed consent.

PROCEDURES. In the COMFORTABLE trial, patients were randomly assigned on a 1:1 basis to treatment with biolimus-eluting stents made of a biodegradable polylactic acid polymer (BioMatrix, Biosensors Europe SA, Morges, Switzerland) or bare metal stents of otherwise identical design (Gazelle, Biosensors Europe SA). In SPUM-ACS STEMI patients, the use of a newer generation drug-eluting stent was recommended with the final selection of stent type left to the discretion of the operator. Before stent implantation, thrombus aspiration was recommended in all patients whenever aspiration was deemed technically feasible (COMFORTABLE) or whenever thrombus was angiographically visible (SPUM-ACS). During the procedure, unfractionated heparin was administered at a dose of at least 5,000 IE or 70 to 100 IE/kg or alternatively bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. There was no recommendation regarding the access route.

DRUG REGIMEN. In the COMFORTABLE study, acetylsalicylic acid (≥250 mg) was administered before the procedure. The administration of a $P2Y_{12}$ inhibitor loading dose (prasugrel 60 mg when available or, alternatively, clopidogrel 600 mg) was recommended as soon as the diagnosis of a STEMI was confirmed by pre-hospital electrocardiography. In centers where prasugrel was available, a loading dose of 60 mg, irrespective of pre-treatment with clopidogrel, was systematically administered, followed by a maintenance dose of 10 mg daily. Prasugrel, in addition to a loading dose of clopidogrel, was administered in the cath lab just before, during, or immediately after primary PCI. Whenever clopidogrel was continued, a daily dose of 75 mg was used. In the SPUM-ACS cohort study, acetylsalicylic acid (≥250 mg) was administered before the procedure, and prasugrel was available at all SPUM-ACS centers since inclusion of the first patient. Administration of a $P2Y_{12}$ inhibitor loading dose (prasugrel 60 mg, when available or, alternatively, clopidogrel 600 mg) was recommended as soon as the diagnosis of a STEMI was confirmed by a pre-hospitalization 12-lead electrocardiogram. The use of an initial loading dose of prasugrel 60 mg was recommended in all patients irrespective of pre-treatment with clopidogrel, followed by a daily dose of 10 mg. Prasugrel, in addition to a loading dose of clopidogrel, was administered in the cath lab just before, during, or immediately after primary PCI. Whenever clopidogrel was continued, a daily dose of 75 mg was prescribed. In patients 75 years of age or older or those with a body weight <60 kg, a prasugrel loading dose of 30 mg followed by a maintenance dose of 5 mg daily was recommended in both studies. Dual antiplatelet therapy was prescribed for at least 1 year in all patients. Study groups were defined according to the specific loading regimen: 1) clopidogrel and a subsequent prasugrel loading dose; and 2) prasugrel loading dose alone. Patients who had prasugrel subsequently replaced by clopidogrel or vice versa were categorized according to the initial loading dose regimen.

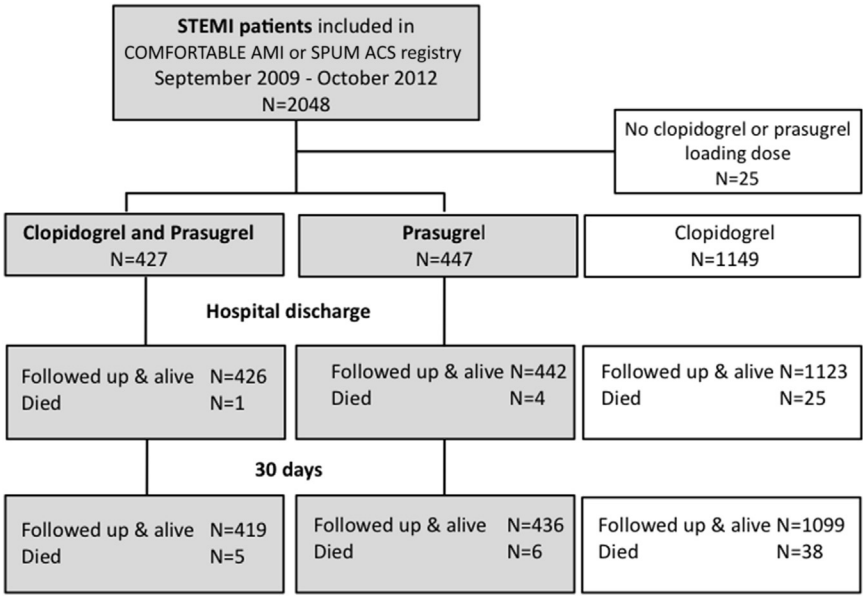
DATA MANAGEMENT. Independent study monitors verified source data according to a pre-specified monitoring plan in the COMFORABLE and SPUM-ACS trials. Identical case record forms were used, and data were stored in the same central database (Cardiobase, CTU and Department of Cardiology, Bern University Hospital, Switzerland and 2mT, Ulm, Germany). Follow-up was scheduled at 30 days and 1 year.

CLINICAL ENDPOINTS. The primary safety endpoint was BARC types 3 to 5 bleeding at 30 days, and the secondary efficacy endpoint was cardiac death, nonfatal myocardial infarction, or stroke at 30 days. Events were adjudicated by an independent clinical

events committee. Endpoint definitions for both COMFORTABLE and SPUM-ACS patients were identical. Bleeding was categorized according to the consensus report from the BARC (11). In addition, bleeding was classified according to the established Thrombolysis In Myocardial Infarction (TIMI) (12) and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial (13) definitions. All deaths were considered cardiac unless an unequivocal noncardiac cause was established. Definitions applied for spontaneous and periprocedural myocardial infarction are listed in the Online Appendix. Ischemic stroke was defined as rapidly developing clinical signs of focal or global disturbance of cerebral function lasting longer than 24 h with imaging of an acute clinically relevant brain lesion. Ischemic cerebral infarctions with conversion to hemorrhage were categorized as ischemic stroke. Intracerebral hemorrhage had to be confirmed by cerebral imaging. Stent thrombosis was defined according to the Academic Research Consortium definitions (14).

STATISTICAL ANALYSIS. Categorical variables are presented as number (%), with p values from a chi-square or Fisher exact test and continuous variables as mean ± SD, with p values from a pairwise Student *t* test. Cox regression analysis of outcomes at hospital discharge and 30-day follow-up using time to first event or composite events were used to compare the clopidogrel and a subsequent prasugrel loading dose versus a prasugrel loading dose alone groups. We report hazard ratios (HRs) with 95% confidence intervals (CIs), both crude, and adjusted as follows. 1) Ten datasets were created by multiple imputation of missing data using chained equations. 2) In each dataset, an inverse probability of treatment weighted (IPTW) was calculated using variables related, with $p < 0.1$, to the 3 exposure groups in the original dataset (where the multinomial treatments are the exposure to clopidogrel and a subsequent prasugrel loading dose or prasugrel or clopidogrel alone). The following baseline variables were used for the IPTW: age, sex, weight, body mass index, hypertension, cholesterolemia, family history of coronary artery disease, peripheral arterial disease, history of stroke or transient ischemic attack, history of malignancy, renal failure (estimated glomerular filtration rate <60), pain onset within 24 h, resuscitation, acute myocardial infarct location, and procedural medications including unfractionated heparin, bivalirudin, low molecular weight heparin, and glycoprotein II/IIIa antagonists. 3) Additional covariates not covered by the IPTW and related, with $p < 0.1$, to BARC types 3 to 5 bleeding (which were history of coronary artery

FIGURE 1 Flow Chart



STEMI = ST-segment elevation myocardial infarction.

TABLE 1 Baseline Characteristics

	Clopidogrel + Prasugrel (n = 427)	Prasugrel (n = 447)	p Value*
Age, yrs	59.8 ± 11.0	58.5 ± 11.0	0.08
Male	358 (83.8)	376 (84.1)	0.93
Body mass index, kg/m^2	27.4 ± 4.4	27.5 ± 4.2	0.59
Cardiovascular risk factors			
Diabetes mellitus	53 (12.4)	57 (12.8)	0.92
Insulin dependent	11 (2.6)	11 (2.5)	1.00
Hypertension	198 (46.4)	206 (46.1)	0.95
Hypercholesterolemia	214 (50.4)	268 (60.2)	0.004
Current smoker	204 (48.3)	220 (49.8)	0.68
Family history of CAD	92 (21.9)	106 (24.1)	0.47
Renal failure	21 (5.0)	49 (11.0)	0.001
Previous MI	36 (8.5)	29 (6.5)	0.30
Previous PCI	42 (9.8)	32 (7.2)	0.18
Previous CABG	12 (2.8)	8 (1.8)	0.37
Bleeding risk assessment			
Age >75 yrs, history of stroke, or weight <60 kg	53 (12.4)	40 (8.9)	0.10
Laboratory findings			
Anemia†	59 (14.5)	62 (14.7)	1.00
Thrombocytopenia‡	24 (5.9)	15 (3.6)	0.14
Clinical presentation			
Time from symptom onset to balloon inflation ≤24 h	93.2	94.2	0.58
Killip class III/IV	15 (3.5)	24 (5.4)	0.19
Left ventricular ejection fraction§	48.9 ± 10.7	49.7 ± 10.4	0.32
Electrocardiographic localization of MI			0.12
Anterior	155 (37.7)	188 (44.9)	
Lateral	19 (4.6)	12 (2.9)	
Inferior	214 (52.1)	203 (48.2)	
Posterior or posterior and lateral	23 (5.6)	17 (4.1)	
Right ventricular MI	32 (7.8)	23 (5.5)	0.21
Lesion complexity			
Bifurcation treatment in any lesion	54 (12.7)	61 (13.9)	0.62
Long lesion (≥28 mm)‖	173 (41.3)	174 (40.4)	0.83

Values are mean ± SD or n (%). *p values pairwise (prasugrel + clopidogrel vs. prasugrel alone) from chi-square, Fisher exact, Student *t* test, or Mann-Whitney *U* test. †Anemia was defined as a hemoglobin concentration <120 g/l for women and <130 g/l for men, according to the definition of the World Health Organization. ‡Thrombocytopenia was defined as <150,000 platelets/μl. §Left ventricular function as assessed by angiography at the time point of presentation or by echocardiography if angiography was not available. ‖Long lesion indicates any lesion treated with a summed stent length of ≥20 mm.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

bypass grafting, left ventricular ejection fraction) or related, with $p < 0.1$, to the composite of cardiac death, reinfarction, or stroke (which were insulin-dependent diabetes, anemia, thrombocytopenia, and Killip III or IV) were selected. 4) The adjusted models on the multiple imputed datasets show HRs weighting each patient with their IPTW and correcting for the additional covariates study, history of coronary artery bypass grafting, left ventricular ejection fraction, insulin-dependent diabetes, anemia, thrombocytopenia, and Killip III or IV. Risk ratios with a continuity correction (with 95% CI) and p values from the Fisher exact test are reported in case of zero events. Adjusted analyses were performed of the 2 primary outcomes only for in-hospital events due to the low number of events during the in-hospital time period. All statistical analyses were 2-sided (with $\alpha = 0.05$) and were performed with Stata 12.1 (StataCorp, College Station, Texas).

RESULTS

PATIENT POPULATION. A total of 2,048 STEMI patients undergoing primary PCI in the context of the COMFORTABLE and the SPUM-ACS trials were included between September 2009 and October 2012 at 12 international sites. A total of 25 patients were excluded because they did not receive either a prasugrel or a clopidogrel loading dose. A total of 427 patients (21.1%) (258 COMFORTABLE and 169 SPUM-ACS participants) received first a loading dose of clopidogrel at the time of first medical contact followed by a subsequent loading dose of prasugrel before, during, or immediately after primary PCI (clopidogrel and a subsequent prasugrel loading dose group). A total of 447 patients (22.1%) (212 COMFORTABLE and 235 SPUM-ACS participants) received a loading dose of prasugrel at the time of first medical contact or before, during, or immediately after primary PCI (prasugrel alone group). The remaining 1,149 patients (56.8%) (668 COMFORTABLE and 463 SPUM-ACS participants) received a loading dose of clopidogrel at the time of first medical contact or before, during, or immediately after primary PCI and were not considered for the primary analysis. Follow-up at 30 days was completed in 98.1% of patients receiving clopidogrel and a subsequent loading dose of prasugrel and 97.5% of patients receiving prasugrel alone (Figure 1). Baseline characteristics of the 2 groups are presented in Table 1. Patients receiving clopidogrel and a subsequent loading dose of prasugrel tended to be older and less frequently had dyslipidemia and renal failure. Procedural characteristics are shown in Table 2. The baseline TIMI flow tended to be improved in patients receiving clopidogrel and a subsequent prasugrel loading dose, and the average stent diameter was smaller in the group receiving clopidogrel and a subsequent loading dose of prasugrel.

LOADING DOSE REGIMEN. Medications before, during, or immediately after the primary PCI, at the time of hospital discharge, at 30 days, and at 1-year follow-up are summarized in Table 3, including details regarding loading and maintenance doses. Bivalirudin and glycoprotein IIb/IIIa were less frequently

used in the group receiving clopidogrel and a subsequent loading dose of prasugrel compared with prasugrel alone patients. At discharge, both groups of patients were prescribed acetylsalicylic acid. More patients receiving clopidogrel and a subsequent loading dose of prasugrel than patients receiving prasugrel alone were kept on prasugrel until hospital discharge (96% and 88.9%, respectively; $p < 0.001$), a difference that was no longer significant at 1 year (81.8% and 78.0%, respectively; $p = 0.19$). A total of 53 of 420 patients receiving clopidogrel and a subsequent loading dose of prasugrel (12.4%) and 40 of 447 (8.9%) ($p = 0.10$) prasugrel alone patients were at an increased risk of bleeding and were therefore fulfilling a formal contraindication to the use of prasugrel (Table 3).

CLINICAL OUTCOMES. Safety. At hospital discharge, the primary safety endpoint of BARC types 3 to 5 bleeding was recorded in 1.4% of patients receiving clopidogrel and a subsequent loading dose of prasugrel and 3.4% of prasugrel alone patients, respectively (adjusted HR: 0.43; 95% CI: 0.17 to 1.08; $p = 0.07$) (Table 4). At 30 days, the primary safety endpoint of BARC types 3 to 5 bleeding was recorded in 1.9% of patients receiving clopidogrel and a subsequent loading dose of prasugrel and 3.4% of patients receiving prasugrel alone (adjusted HR: 0.57; 95% CI 0.25 to 1.30; $p = 0.18$) (Table 5). Similarly, no differences in TIMI major (1.2% vs. 1.8%) or TIMI minor (0.7% vs. 1.6%), and GUSTO severe (0.5% vs. 1.3%) or GUSTO moderate (0.5% vs. 0.5%) bleeding episodes were observed at 30 days (Table 5), and there were no differences in terms of bleeding localization (Table 6). To address potential differences in bleeding risk between patients receiving clopidogrel and a subsequent loading dose of prasugrel and those receiving prasugrel alone at the time point of inclusion, we assessed the HAS-BLED bleeding score in both treatment groups and found no significant difference but a trend toward a lower bleeding risk in patients receiving prasugrel alone. When adjusting the primary safety endpoint using the HAS-BLED score, we found consistent results (BARC types 3 to 5 bleeding at 30 days: adjusted HR [clopidogrel and a subsequent loading dose of prasugrel vs. prasugrel alone]: 0.54; 95% CI: 0.23 to 1.27; $p = 0.16$) (Online Table 1).

One-year safety results are shown in Online Table 2. The primary safety endpoint at 1 year was observed in 3.9% of patients receiving clopidogrel and a subsequent loading dose of prasugrel and 4.3% of patients receiving prasugrel alone (adjusted HR: 0.91; 95% CI: 0.46 to 1.79; $p = 0.79$).

TABLE 2 Procedural Characteristics

	Clopidogrel + Prasugrel (n = 427)	Prasugrel (n = 447)	p Value*
No. of lesions treated	602	566	
Lesions treated	1.41 ± 0.73	1.28 ± 0.60	0.003
Treated vessels			
Left main coronary artery	7 (1.6)	2 (0.5)	0.10
Left anterior descending artery	185 (43.4)	209 (47.2)	0.28
Left circumflex artery	85 (20.0)	73 (16.5)	0.19
Right coronary artery	200 (46.9)	184 (41.5)	0.12
Bypass graft	2 (0.5)	2 (0.5)	1.00
Intravenous vasopressors	10 (2.3)	13 (2.9)	0.68
Baseline TIMI flow in infarct vessel			0.05
0 or 1	329 (54.9)	332 (61.5)	
2	99 (16.5)	68 (12.6)	
3	171 (28.5)	140 (25.9)	
Primary PCI procedure			
No. of stents per lesion	1.32 ± 0.64	1.26 ± 0.53	0.34
Type of stent			
Drug-eluting stent	401 (70.2)	359 (69.0)	0.79
Bare metal stent	172 (30.1)	162 (31.2)	0.76
Total stent length per lesion, mm	25.1 ± 13.70	25.8 ± 12.7	0.75
Average stent diameter, mm	3.1 ± 0.5	3.2 ± 0.7	0.06
Direct stenting	154 (27.0)	189 (36.4)	0.65
Maximal balloon pressure, atm	14.5 ± 3.7	14.5 ± 3.6	0.87
Overlapping stents implanted	135 (23.6)	110 (21.2)	0.33
Successful thrombus aspiration†	131 (30.7)	163 (36.5)	0.71
Final TIMI flow in infarct vessel			0.78
0 or 1	4 (0.7)	6 (1.1)	
2	20 (3.3)	18 (3.2)	
3	577 (96.0)	531 (95.7)	

Values are mean ± SD or n (%). Patients grouped according to the loading dose, already on a daily maintenance dose, or immediate post-procedure exposure. *p values pairwise (prasugrel + clopidogrel vs. prasugrel alone) from chi-square, Fisher exact test, or *t* test; p values from mixed models accounting for lesions nested within patients for lesion-level data. †Visible thrombus obtained.

PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

A comparison of patients receiving clopidogrel and a subsequent loading dose of prasugrel with those receiving clopidogrel only was not the primary focus of this study; however, the 30-day outcomes are provided in Online Table 3. The frequency of the primary endpoint of BARC types 3 to 5 bleeding was not different between patients receiving clopidogrel and a subsequent loading dose of prasugrel (1.9%) compared with patients receiving clopidogrel alone (3%) (adjusted HR: 0.87; 95% CI: 0.38 to 1.97; $p = 0.73$).

EFFICACY. The frequency of the secondary efficacy endpoint, a composite of cardiac death, nonfatal myocardial infarction, and stroke at hospital discharge, occurred less frequently in the group receiving clopidogrel and a subsequent loading dose of prasugrel compared with the prasugrel alone group (0.23% vs. 2.0%; adjusted HR: 0.07: 95%

TABLE 3 Periprocedural and Follow-up Medication

	Clopidogrel+ Prasugrel (n = 427)	Prasugrel (n = 447)	p Value*
Medication during primary PCI			
Unfractionated heparin	409 (95.8)	360 (80.7)	<0.001
Bivalirudin	51 (11.9)	105 (23.5)	<0.001
GP IIb/IIIa antagonist	124 (29.0)	178 (39.9)	0.001
Loading doses, mg			<0.001
Clopidogrel alone	1 (0.2)†	0 (0.0)	
300	38 (9.0)		
600	380 (89.6)		
Other	3 (0.7)		
N/A	3 (0.7)		
Prasugrel alone	3 (0.7)‡	430 (96.2)	<0.001
30	46 (10.8)	6 (1.4)	<0.001
60	370 (86.9)	435 (97.3)	<0.001
Other	8 (1.9)	3 (0.7)	0.14
N/A	2 (0.5)	3 (0.7)	1.00
Both clopidogrel and prasugrel	424 (99.1)	0 (0.0)	<0.001
1 week double clopidogrel dose	1 (0.2)	0 (0)	N/A
At discharge			
Aspirin	423 (99.5)	440 (99.5)	1.00
Prasugrel	408 (96.0)	393 (88.9)	<0.001
Clopidogrel	16 (3.8)	39 (8.8)	0.003
Any DAPT	422 (99.3)	433 (98.0)	0.14
At 30 days			
Aspirin	414 (99.0)	432 (99.3)	0.72
Prasugrel	384 (91.9)	376 (86.4)	0.01
Clopidogrel	38 (9.1)	49 (11.3)	0.31
Any DAPT	413 (98.8)	420 (96.6)	0.04
At 1 year			
Aspirin	392 (98)	412 (96.5)	0.209
Prasugrel	327 (81.8)	333 (78.0)	0.19
Clopidogrel	42 (10.5)	47 (11.0)	0.82
Any DAPT	362 (90.5)	376 (88.1)	0.26
High-risk patients (age ≥75 yrs or weight <60 kg, or history of stroke/TIA)*§	n = 53	n = 40	
Clopidogrel loading dose, mg	n = 52		
300	2 (3.8)		
600	48 (92.3)		
Other	1 (1.9)		
N/A	1 (1.9)		
Prasugrel loading dose, mg	n = 53	n = 38	0.680
30	1 (1.9)	0 (0.0)	1.000
60	50 (94.3)	37 (97.4)	0.638
Other	1 (1.9)	0 (0.0)	1.000
N/A	1 (1.9)	1 (2.6)	1.000

Values are n (%). Patients grouped according to the loading dose, already on daily maintenance dose MD, or immediate post-procedure exposure. *p values (prasugrel + clopidogrel vs. prasugrel alone) from chi-square or Fisher exact test. †Already on maintenance dose of prasugrel. ‡Already on maintenance dose of clopidogrel. Number of patients who received loading dose of prasugrel or clopidogrel. Excludes patients without any loading. §Excludes 19 patients with the weight missing, but all 19 were assumed low risk because all 19 were younger than 75 years of age and did not have a history of stroke.

DAPT = dual antiplatelet therapy; GP = glycoprotein; N/A = not available; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

CI: 0.01 to 0.55; p = 0.01) (Table 4). However, there was no longer a difference observed at 30 days (1.9% vs. 2.9%; adjusted HR: 0.66; 95% CI: 0.27 to 1.62; p = 0.36) (Table 5) between groups. No differences in individual endpoints such as death, cardiac death, nonfatal MI, and stroke were observed at 30 days. There was no difference in the rate of definite or probable stent thrombosis both at hospital discharge and 30 days. One-year efficacy data are shown in the Online Table 2.

DISCUSSION

We report the results of the largest retrospective cohort study of prospectively collected data investigating the clinical safety (and efficacy) of concomitant prasugrel and clopidogrel loading compared with prasugrel loading alone in patients with STEMI undergoing primary PCI. At hospital discharge and 30-day follow-up, the concomitant administration of prasugrel and clopidogrel loading doses was not associated with an increased risk of severe bleeding as assessed by the primary safety parameter, BARC types 3, 4, and 5 bleeding. Likewise, no differences in TIMI major or minor and GUSTO severe or moderate bleeding were observed. In addition, a similar efficacy of the 2 treatment groups was confirmed.

Pretreatment with $P2Y_{12}$ inhibitors in STEMI patients is recommended by guidelines (6). With regard to the choice of agent, current guidelines indicate a preference for novel $P2Y_{12}$ inhibitors over clopidogrel (7,8) because of their more rapid, more potent, and consistent inhibition of platelet aggregation as well as improved clinical outcomes (4,15). Thus, prasugrel has been shown to be superior to clopidogrel in the prevention of recurrent ischemic events in patients with ACS and known coronary anatomy at the expense of an increased risk of TIMI major bleeding in the large-scale TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) (16). Prasugrel was effective among the subgroup of STEMI patients, potentially related to the high residual on-treatment platelet reactivity in clopidogrel-treated STEMI patients (17). However, many patients with STEMI are still pre-treated with clopidogrel at the time of first medical contact before primary PCI, posing the question of whether these patients should undergo additional loading with prasugrel followed by prasugrel maintenance or be maintained on clopidogrel alone. Although one would expect at least similar efficacy, concerns relate to an excess risk of bleeding with the double-loading regimen. As major bleeding is recognized to affect clinical outcomes including survival (18), any benefit in terms of efficacy may be camouflaged by the increased risk of bleeding.

TABLE 4 Clinical Outcomes at Hospital Discharge

	C + P Events (n = 427)	P Events (n = 447)	Crude Analyses		IPTW Adjusted Analyses	
			CP vs. P, HR (95% CI)	p Value	CP vs. P, HR (95% CI)	p Value
BARC types 3-5 bleeding	6 (1.41)	15 (3.36)	0.44 (0.18–1.08)	0.07	0.43 (0.17–1.08)	0.07
Cardiac death, nonfatal myocardial infarction, or stroke	1 (0.23)	9 (2.01)	0.14 (0.02–0.99)	0.05	0.07 (0.01–0.55)	0.01
Death	1 (0.23)	4 (0.89)	0.31 (0.04–2.30)	0.25		
Cardiac death	1 (0.23)	3 (0.67)	0.40 (0.05–3.11)	0.38		
Myocardial infarction	0 (0.00)	4 (0.89)	0.21 (0.02–1.79)	0.13		
Any revascularization	2 (0.47)	6 (1.34)	0.35 (0.08–1.60)	0.18		
Definite stent thrombosis	0 (0.00)	2 (0.45)	0.35 (0.04–3.35)	0.50		
Definite or probable stent thrombosis	0 (0.00)	6 (1.34)	0.15 (0.02–1.21)	0.03		
Stroke	0 (0.00)	2 (0.45)	0.35 (0.04–3.35)	0.50		
BARC bleeding type						
3	5 (1.17)	13 (2.91)	0.42 (0.15–1.12)	0.08		
3a	3 (0.70)	7 (1.57)	0.45 (0.12–1.73)	0.25		
3b	2 (0.47)	6 (1.34)	0.37 (0.08–1.66)	0.20		
3c	0 (0.00)	0 (0.00)				
4	0 (0.00)	1 (0.22)	0.52 (0.05–5.71)	1.00		
5	1 (0.23)	1 (0.22)	1.07 (0.09–12.40)	0.96		
TIMI bleeding						
Major	3 (0.70)	8 (1.79)	0.42 (0.13–1.44)	0.17		
Minor	3 (0.70)	7 (1.57)	0.45 (0.12–1.73)	0.25		
GUSTO bleeding						
Severe	1 (0.23)	6 (1.34)	0.18 (0.02–1.40)	0.10		
Moderate	1 (0.23)	2 (0.45)	0.58 (0.07–4.93)	0.61		

Values are n (%) unless otherwise indicated. Incidence rate ratios (95% CI), and p Values from Poisson regressions (crude analyses) or Poisson regressions weighted by inverse probability of treatment weighted and adjusted for study (COMFORTABLE or BIOMARKER), insulin-dependent diabetes, history of coronary artery bypass grafting, anemia, thrombocytopenia, Killip III or IV, left ventricular ejection fraction after 10 times multiple imputation of missing values using chained equations (adjusted analyses). Risk ratio with continuity correction and Fisher exact test p values are reported in case of zero events in 1 treatment group. The inverse probability of treatment weighted was calculated using the following baseline variables: age, sex, diabetes, hypercholesterolemia, current smoker, family history of coronary artery disease, previous coronary artery bypass grafting, pain onset within 24 h, acute myocardial infarction location, stent type, and procedural medications including unfractionated heparin, bivalirudin, low molecular weight heparin, GPII/IIIa antagonists.

BARC = Bleeding Academic Research Consortium; C = clopidogrel; CI = confidence interval; CP = clopidogrel and a subsequent prasugrel loading dose; HR = hazard ratio; IPTW = inverse probability of treatment weighted; P = prasugrel.

Given this background, our findings showing no increase in bleeding rates according to any bleeding classification including BARC types 3 to 5 bleeding, major or minor TIMI, and GUSTO severe or moderate irrespective of loading regimen are reassuring and suggest a wide range of safety of these agents as used in routine clinical practice. The notion that additional loading with potent platelet inhibitors appears safe among STEMI patients undergoing primary PCI is further substantiated by the concomitant use of glycoprotein IIB/IIIa antagonists during primary PCI in 29% of patients in the group receiving clopidogrel and a subsequent loading dose of prasugrel and 40% of patients in the prasugrel alone group.

Prasugrel inhibits platelet activation through irreversible $P2Y_{12}$ receptor blockade with a mechanism similar to that of clopidogrel. Four pharmacodynamic studies have investigated the switch from clopidogrel to prasugrel under various circumstances. The SWAP (Switching Anti Platelet) study assessed the effect of a prasugrel loading dose in patients receiving a clopidogrel maintenance dose for at least 10 days (19). An additional loading dose resulted in a further significant reduction in platelet function within 2 h of administration. In the ACAPULCO (Prasugrel Compared With High-Dose Clopidogrel in acute coronary syndrome) study, a prasugrel maintenance dose regimen resulted in significantly greater platelet inhibition compared with clopidogrel at a double maintenance dose (180 mg) after a loading dose of 900 mg clopidogrel in both groups (5). Two recent studies investigated the effect of a concomitant loading dose with both clopidogrel and prasugrel compared with prasugrel alone in ACS patients. An observational study performed in 47 STEMI patients observed a profound inhibition of platelet aggregation after concomitant loading with both clopidogrel and prasugrel (median [interquartile range]: 10 [8 to 31] platelet reactivity units (PRUs), which, however, was similar to that of patients loaded with prasugrel alone (median [interquartile range]: 9 [6 to 60] PRUs; p = 0.916), suggesting no excess in platelet inhibition after dual loading (20). In the TRIPLET (Transferring From

TABLE 5 Clinical Outcomes at 30 Days

	CP Events (n = 427)	P Events (n = 447)	Crude Analyses		IPTW Adjusted Analyses	
			CP vs. P, HR (95% CI)	p Value	CP vs. P, HR (95% CI)	p Value
BARC types 3-5 bleeding	8 (1.9)	15 (3.4)	0.57 (0.24-1.34)	0.20	0.57 (0.25-1.30)	0.18
Cardiac death, nonfatal myocardial infarction, or stroke	8 (1.9)	13 (2.9)	0.70 (0.29-1.70)	0.44	0.66 (0.27-1.62)	0.36
Death	5 (1.2)	6 (1.4)	0.99 (0.30-3.28)	0.99	1.05 (0.27-4.10)	0.95
Cardiac death	5 (1.2)	5 (1.1)	1.18 (0.34-4.10)	0.78	1.05 (0.27-4.10)	0.95
Myocardial infarction	2 (0.5)	5 (1.1)	0.41 (0.08-2.11)	0.28	0.57 (0.14-2.21)	0.41
Any revascularization	9 (2.1)	9 (2.0)	1.06 (0.42-2.70)	0.90	1.46 (0.49-4.32)	0.50
Definite ST	2 (0.5)	2 (0.4)	1.07 (0.15-7.71)	0.95	0.98 (0.22-4.39)	0.98
Definite or probable ST	5 (1.2)	7 (1.6)	0.82 (0.26-2.61)	0.74	0.89 (0.28-2.87)	0.85
Stroke	1 (0.2)	3 (0.7)	0.46 (0.05-4.38)	0.50	0.47 (0.04-5.98)	0.56
BARC bleeding type						
3	7 (1.6)	13 (2.9)	0.57 (0.22-1.43)	0.23	0.61 (0.25-1.48)	0.28
3a	3 (0.7)	7 (1.6)	0.45 (0.12-1.76)	0.25	0.44 (0.11-1.75)	0.24
3b	4 (0.9)	6 (1.3)	0.71 (0.20-2.53)	0.59	0.81 (0.25-2.67)	0.74
3c	0 (0.0)	0 (0.0)				
4	0 (0.0)	1 (0.2)	0.52 (0.05-5.71)	1.00		
5	1 (0.2)	2 (0.5)	0.49 (0.04-5.44)	0.56	0.33 (0.03-4.35)	0.40
TIMI bleeding						
Major	5 (1.2)	8 (1.8)	0.67 (0.22-2.08)	0.49	0.68 (0.24-1.92)	0.46
Minor	3 (0.7)	7 (1.6)	0.45 (0.12-1.76)	0.25	0.44 (0.11-1.75)	0.24
GUSTO bleeding						
Severe	2 (0.5)	6 (1.3)	0.35 (0.07-1.74)	0.20	0.27 (0.06-1.25)	0.09
Moderate	2 (0.5)	2 (0.5)	1.07 (0.15-7.71)	0.95	1.73 (0.28-10.51)	0.55

Values are n (%) unless otherwise indicated. Incidence rate ratios (95% confidence interval CI) and p values from Poisson regressions (crude analyses) or Poisson regressions weighted by the inverse probability of treatment weighted and adjusted for study (COMFORTABLE or BIOMARKER), insulin-dependent diabetes, history of coronary artery bypass grafting, anemia, thrombocytopenia, Killip III or IV, left ventricular ejection fraction after 10 times multiple imputation of missing values using chained equations (adjusted analyses). Risk ratio with continuity correction and Fisher exact test p values are reported, in case of zero events in one treatment group. The inverse probability of treatment weighted was calculated using the following baseline variables: age, sex, diabetes, hypercholesterolemia, current smoker, family history of coronary artery disease, previous coronary artery bypass grafting, pain onset within 24 h, acute myocardial infarction location, stent type, and procedural medications including unfractionated heparin, bivalirudin, low molecular weight heparin, glycoprotein II/IIIa antagonists

ST = stent thrombosis; other abbreviations as in Tables 2 and 4.

Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome PatiEnTs study, 282 ACS patients were included to assess the pharmacodynamic response to prasugrel alone compared with prasugrel 60 mg or 30 mg added <24 h to a loading dose of 600 mg clopidogrel. Consistent with the aforementioned observational study, no significant increase in PRUs was observed with prasugrel (57.9 PRUs) compared with prasugrel in addition to a clopidogrel loading dose (35.6 PRUs), a least-square mean difference (95% CI) of 22.2 (−11.1 to 55.5) (p = 0.19) (21).

TABLE 6 Bleeding Location at 30-Day Follow-up

Location	CP (n = 9)	P (n = 18)	p Value (CP vs. P)
			0.50
Intracranial	0 (0)	0 (0)	
Intraocular	0 (0)	0 (0)	
Retroperitoneal	0 (0)	4 (22)	
Vascular access site	6 (67)	5 (28)	
Gastrointestinal	1 (11)	2 (11)	
Genitourinary	1 (11)	3 (17)	
Pulmonary	0 (0)	1 (6)	
Pericardial	0 (0)	1 (4)	
Other	1 (11)	2 (12)	

Values are n (%).

Abbreviations as in Table 4.

The absence of excessive levels of platelet inhibition observed in pharmacodynamic studies after the administration of a concomitant loading dose of prasugrel in addition to clopidogrel compared with a prasugrel loading dose alone provides a solid explanation for the absence of an excess in clinically overt bleeding in the treatment group receiving a double loading. The treatment with a full loading dose of prasugrel alone almost completely saturates the $P2Y_{12}$ receptor according to pharmacodynamic studies (22). In patients who have been pretreated with a full loading dose of clopidogrel, the addition of a loading dose of prasugrel will occupy the remaining $P2Y_{12}$ receptor sites not completely saturated by the active metabolite of clopidogrel. However, the difference between a strategy of loading with prasugrel alone compared with additional

prasugrel loading after a clopidogrel loading dose will result only in a minor difference in actual platelet inhibition.

Radial access is associated with a lower risk of access site bleeding in STEMI patients (23). In the present study, only 2 centers preferentially used a radial access route, limited to 155 patients. When we performed a sensitivity analysis excluding the 2 centers preferentially using a radial access route, we found similar hazards of bleeding between groups.

In the present study, the dual-loading regimen of prasugrel and clopidogrel as well as loading with prasugrel alone were associated with a similar efficacy as indicated by the secondary composite endpoint of cardiac death, myocardial infarction, and stroke. In addition, no differences in definite or probable stent thrombosis were noted.

The comparison of patients receiving clopidogrel and a subsequent loading dose of prasugrel with patients receiving only a clopidogrel loading dose was not the primary focus of this analysis in view of the available evidence of the TRITON-TIMI-38. Moreover, this comparison is scientifically less valid as it was influenced by unmeasured confounding such that patients with a high bleeding risk did not receive a concomitant loading dose of prasugrel. However, outcomes confirm the absence of an excess in bleeding in patients receiving clopidogrel and a subsequent loading dose of prasugrel compared with those receiving only clopidogrel.

STUDY LIMITATIONS. The results of this observational, nonrandomized study have to be interpreted in the light of the following limitations. Patients were not randomly allocated to treatment groups, and findings should therefore be carefully interpreted. As the treatment allocation was at the discretion of the operator, patients with high bleeding risk were prevented from receiving a double-loading dose. Even after statistical adjustment for baseline clinical characteristics, HRs indicated a higher bleeding risk (with CIs crossing the line of no difference) in patients receiving prasugrel alone compared with patients receiving clopidogrel and a subsequent loading dose of prasugrel. To further explore a potential difference in the baseline bleeding risk, we assessed the HAS-BLED bleeding score in all patients and found a trend toward a higher bleeding risk in patients receiving prasugrel alone compared with those receiving clopidogrel and a subsequent loading dose of prasugrel. When adjusting the primary safety endpoint results for the HAS-BLED bleeding score, results remained robust. Despite pre-specified recommendations regarding the use of prasugrel and clopidogrel in STEMI patients included in the present study, the final decision was left to the discretion of the treating physician. The sample size of this analysis was not on the basis of a pre-specified power calculation, and therefore the absence of differences in bleeding events between groups may reflect the lack of sufficient power. The number of bleeding events was low, with a total of 24 bleeding events (8 in those receiving clopidogrel and a subsequent loading dose of prasugrel and 15 in those receiving prasugrel alone). As a result, CIs describing differences in the primary safety endpoint were wide, indicating no significant difference between groups. Notwithstanding, this is thus far the largest observational cohort, including 428 patients with concomitant loading of prasugrel and clopidogrel whose relevance is magnified due to the lack of randomized clinical trials addressing the safety of dual loading-dose regimens. In addition, only a few exclusion criteria were applied in both studies and 12 international sites participated, which increases the generalizability of the results.

CONCLUSIONS

The findings of our study are clinically relevant as many STEMI patients referred for primary PCI are pre-treated with clopidogrel in routine clinical practice. On the basis of the presented data, the addition of a prasugrel loading dose in clopidogrel pre-treated patients may be considered to achieve more rapid, more potent, and consistent inhibition of platelet aggregation. This treatment strategy does not seem to result in excess bleeding although it has the potential to lower the risk of ischemic adverse events, as previously shown. Notwithstanding, dose adaptations and attention to relative and absolute contraindications for the use of prasugrel should be carefully weighed in the therapeutic decision process.

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PERSPECTIVES

WHAT IS KNOWN? Pharmacodynamic studies do not show an excess in platelet inhibition after double loading doses of clopidogrel and prasugrel. However, safety data regarding a double-loading regimen with prasugrel and clopidogrel are not available.

WHAT IS NEW? This is the largest observational study in STEMI patients undergoing primary PCI and suggests that a loading dose of prasugrel in STEMI patients pre-loaded with clopidogrel—a scenario frequently encountered in clinical practice—is not associated with an increased risk of major bleeding events.

WHAT IS NEXT? Further studies are needed to corroborate these findings to determine the optimal dual antiplatelet therapy loading strategy in STEMI patients.

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KEY WORDS antiplatelet therapy, clopidogrel, $P2Y_{12}$ inhibitors, prasugrel, ST-segment elevation myocardial infarction

APPENDIX For an expanded Methods section as well as supplemental tables, please see the online version of this article.