

# Real-world clopidogrel utilization in acute coronary syndromes: patients selection and outcomes in a single-center experience

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## Abstract

**Background:** With this study, we sought to identify patient characteristics associated with clopidogrel prescription and its relationship with in-hospital adverse events in an unselected cohort of ACSs patients.

**Materials and Methods:** We studied all consecutive patients admitted at our institution for ACSs from 2012 to 2014. Patients were divided into two groups based on clopidogrel or novel P2Y<sub>12</sub> inhibitors (prasugrel or ticagrelor) prescription and the relationship between clopidogrel use and patient clinical characteristics and in-hospital adverse events was evaluated using logistic regression analysis.

**Results:** The population median age was 68 years (57–77 year) and clopidogrel was prescribed in 230 patients (46%). Patients characteristics associated with clopidogrel prescription were older age, female sex, non-ST-elevation ACS diagnosis, the presence of diabetes mellitus and anemia, worse renal and left ventricular functions and a higher Killip class. Patients on clopidogrel demonstrated a significantly higher incidence of in-hospital mortality (4.8%) than prasugrel and ticagrelor-treated patients (0.4%), while a nonstatistically significant trend emerged considering bleeding events. However, on multivariable logistic regression analysis female sex, the presence of anemia and Killip class were the only variables independently associated with in-hospital death.

**Conclusion:** Patients treated with clopidogrel showed a higher in-hospital mortality. However, clinical variables associated with its use identify a population at high risk for adverse events and this seems to play a major role for the higher in-hospital mortality observed in clopidogrel-treated patients.

**Keywords:** acute coronary syndromes, clopidogrel, dual antiplatelet therapy, prasugrel, ticagrelor

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## Introduction

Since its introduction in the clinical arena, clopidogrel, a P2Y<sub>12</sub> adenosine diphosphate receptor antagonist, has been largely and successfully used in patients with acute coronary syndromes (ACSs), paving the way to dual antiplatelet therapy (DAPT) utilization as the cornerstone of the contemporary management of patients with ACS.<sup>1–6</sup> Clopidogrel, however, has several drawbacks consisting of delayed onset, potential interactions with other drugs, and variable platelet responses

due to genetic polymorphisms.<sup>7,8</sup> In recent years several new antithrombotic treatments have been evaluated and new data regarding novel antiplatelet drugs have been published. In particular, two new P2Y<sub>12</sub> receptor inhibitors, prasugrel and ticagrelor, have been introduced in clinical practice.<sup>9,10</sup> In randomized clinical trials, these two inhibitors resulted to be superior in major cardiac adverse event (MACE) reduction in ACS patients compared to clopidogrel; the latter however, remains largely used in daily clinical practice, as

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described in some large multicenter and single-center observational studies.<sup>11–13</sup>

In this study, we evaluated the patterns of DAPT prescription in an unselected cohort of patients admitted at our institution for ACS. In particular, we sought to identify the clinical variables associated with clopidogrel use and its relationship with in-hospital adverse events.

## Methods and materials

### Study population

All consecutive patients admitted to the Coronary Care Unit (CCU) of the San Paolo Hospital (Milan) with diagnosis of ACS between 2012 and 2014 composed our study population. The diagnosis of ACS was based on new onset ischemia-related symptoms and the presence of at least one of the following criteria: (i) electrocardiographic changes indicative of myocardial ischemia; and (ii) troponin elevation above the 99th percentile threshold of a healthy reference population, with 10% variability coefficient. Patients were classified as having ST-elevation myocardial infarction (STEMI) or non-ST-elevation ACS (NSTEMI-ACS) according to the standardized electrocardiographic criteria.

An all-comers design study was adopted with no restriction on age or on critically ill patients inclusion.

Patients were treated according to usual clinical practice. Coronary angiography and percutaneous coronary intervention (PCI) were performed using standard techniques.

The study complies with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the San Paolo Hospital. For this type of study, a formal consent was not required by the Ethical Committee; however, all the patients signed a standard consent regarding sensitive personal data treatment.

### Data collection and variables definitions

Baseline clinical characteristics, medical history, biochemical variables, angiographic data and pharmacologic and invasive treatments employed during hospitalization were prospectively collected and recorded on a computer

database designed for ACS patients admitted to our CCU. Based on clinical and laboratory data collected at admission, GRACE (Global Registry of Acute Coronary Events)<sup>14</sup> and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA (American College of Cardiology/American Heart Association) Guidelines)<sup>15</sup> risk scores were calculated in order to quantify the risk of in-hospital death and bleeding events. Finally, on the base of the P2Y12 inhibitor prescribed, patients were divided in two groups: those treated with clopidogrel and those treated with prasugrel or ticagrelor.

In-hospital adverse events considered for our analysis were: (i) myocardial infarction/re-infarction (ReMI), diagnosed in the presence of new ischemic symptoms and an elevation or re-elevation of biomarkers of myocardial necrosis with or without concurrent electrocardiographic changes; (ii) urgent percutaneous revascularization (UPR); (iii) bleedings, classified according to the Bleeding Academic Research Consortium (BARC) criteria;<sup>16</sup> and (iv) mortality.

### Statistical analysis

Continuous variables are presented as medians and interquartile ranges and categorical variables are presented as absolute values and percentages. Comparisons between continuous variables were performed using Mann–Whitney or Kruskal–Wallis tests and comparisons between categorical variables were performed using the Chi-squared or Fisher's exact test. Statistical significance was defined as  $p < 0.05$ .

In order to find an association between clinical variables and clopidogrel prescription, univariable logistic regression analysis was performed. All the variables with a  $p$  value  $< 0.05$  at the univariable analysis were included along with clopidogrel prescription in a multivariable stepwise logistic regression analysis to identify the independent predictors of in-hospital adverse events. Results of logistic regression are presented as odds ratios with 95% confidence interval.

MedCalc Statistical Software version 16.2.0 and Graph Pad Prism version 6 were the statistical packages used.

## Results

### *Baseline characteristics*

The study cohort enrolled during the two-year study period consisted of 501 patients (median age 68 years, 31% females), 45% of whom had a STEMI and 55% had a NSTEMI-ACS. Baseline clinical characteristics are summarized in Table 1. No statistically significant difference was found regarding age and sex distribution between the two ACS groups. In the whole population, hypertension was present in 63% of patients, diabetes mellitus in 27%, a history of prior myocardial infarction or PCI in 22% and 18%, respectively, a stage III or higher renal failure in 25%, and a Killip class  $\geq 2$  at admission in 16%. The median GRACE risk score was 139 (113–167) and the median CRUSADE risk score was 27 (15–40). Patients with NSTEMI-ACS presented a significantly higher prevalence of arterial hypertension and diabetes mellitus and had more often a history of coronary artery disease compared with those in the STEMI group. Moreover, they presented at admission a higher prevalence of renal failure and anemia. Finally, the GRACE risk score was higher in STEMI patients, while the CRUSADE score was higher in NSTEMI-ACS group.

### *Clinical management and antithrombotic strategy (Table 1)*

Oral antiplatelet therapy was prescribed as follows: 488 (97%) patients received aspirin and 470 (94%) received a P2Y<sub>12</sub> inhibitor. A total of 31 patients (6%) were treated with aspirin alone or did not receive any antiplatelet treatment. Of the patients treated with DAPT, 230 were on clopidogrel and 240 were on prasugrel or ticagrelor. DAPT was used more often in STEMI than in NSTEMI-ACS patients. Clopidogrel was the most often second antiplatelet agent used both in STEMI (40%) and in NSTEMI-ACS (51%) subgroups. Clopidogrel and ticagrelor were significantly more often used in NSTEMI-ACS patients in contrast to prasugrel which was more often used in STEMI patients. Glycoprotein IIb/IIIa inhibitors and bivalirudin were used more often in STEMI patients, while fondaparinux was used in 100 patients (20%), mostly with NSTEMI-ACS. The majority of patients (95%) underwent coronary angiography and multivessel coronary disease (MVD) was diagnosed in 59% of cases. PCI was performed in 356 patients (75%), significantly more often in the STEMI group. A radial arterial access was used in 56% of cases.

### *Clinical characteristics associated with clopidogrel prescription*

Table 2 summarizes the clinical characteristics of patients according to the P2Y<sub>12</sub> therapy prescribed (clopidogrel *versus* novel P2Y<sub>12</sub> inhibitors). Patients treated with clopidogrel were significantly older, with an age  $\geq 75$  years in 53% of cases *versus* only 11% in patients treated with prasugrel or ticagrelor. They were more frequently females, had a higher prevalence of diabetes, anemia and stage III or higher renal failure. They presented at admission a worse Killip class and a worse in-hospital left ventricular systolic function. Finally, they had more often a NSTEMI-ACS diagnosis and underwent less often to coronary angiography and PCI, although presenting with a higher prevalence of MVD. In summary, comparing the P2Y<sub>12</sub> inhibitors therapy subgroups, clopidogrel patients correspond to a higher risk population for both in-hospital ischemic and hemorrhagic events. In fact, they showed GRACE and CRUSADE risk scores values significantly higher than prasugrel or ticagrelor-treated patients. At the univariable logistic regression analysis some clopidogrel use predictors emerged (Figure 1): advanced age, female sex, diabetes mellitus, renal failure, anemia, atrial fibrillation, MVD, NSTEMI-ACS presentation, worse Killip class, lower ejection fraction and higher GRACE and CRUSADE risk scores were associated with its prescription.

### *In-hospital adverse events and their relationship with clopidogrel use*

Table 3 summarizes the in-hospital major adverse events according to the P2Y<sub>12</sub> therapy prescribed (clopidogrel *versus* novel P2Y<sub>12</sub> inhibitors). In the whole population, the composite incidence of ReMI and UPR was 7%, 32 patients (6.4%) underwent a BARC type 2 or 3 bleeding, 11 (2.2%) a BARC type 3 bleeding, and mortality was 2.6%. Patients treated with clopidogrel presented a significantly higher mortality (4.8%) than patients treated with prasugrel or ticagrelor (0.4%) and a borderline significant higher incidence of overall bleedings, while no significant differences were found regarding ReMI/UPR and BARC type 3 bleedings. In order to further analyze the association of clopidogrel use with mortality and overall bleedings, we performed a stepwise multivariable logistic regression analysis including along with clopidogrel prescription all the variables significantly associated with its use. What we found is that only female sex, the

**Table 1.** Clinical characteristics of the study population. Values are presented as median (interquartile range) or *n* (%).

	Overall <i>n</i> = 501	STEMI <i>n</i> = 225	NSTE-ACS <i>n</i> = 276	<i>p</i> value
Age (years)	68 (57–77)	67 (58–76)	70 (57–78)	0.26
Age ≥ 75 years	165 (33)	67 (30)	98 (35)	0.18
Female	157 (31)	66 (29)	91 (33)	0.38
<b>MEDICAL HISTORY</b>				
Diabetes mellitus	136 (27)	48 (21)	88 (32)	0.008
Hypertension	317 (63)	124 (55)	193 (70)	0.0007
Dyslipidemia	213 (42)	91 (40)	122 (44)	0.39
Active smokers	185 (37)	93 (41)	92 (33)	0.07
Prior MI	108 (22)	22 (10)	86 (31)	<0.0001
Prior PCI	89 (18)	21 (9)	68 (25)	<0.0001
Prior CABG	38 (8)	5 (2)	33 (12)	<0.0001
Prior stroke/TIA	25 (5)	13 (6)	12 (4)	0.53
<b>CLINICAL PRESENTATION</b>				
eGFR < 60 ml/min/m <sup>2</sup>	125 (25)	46 (20)	79 (29)	0.03
Anemia	92 (18)	31 (14)	61 (22)	0.02
EF (%)	54 (45–58)	51 (43–56)	55 (45–60)	<0.0001
Killip class ≥ 2	78 (16)	28 (12)	50 (18)	0.08
Atrial fibrillation	59 (12)	29 (13)	30 (11)	0.49
Acute pulmonary edema	19 (4)	3 (1)	16 (6)	0.009
Cardiogenic shock	12 (2)	9 (4)	3 (1)	0.04
Cardiac arrest	11 (2)	10 (4)	1 (0.4)	0.003
GRACE risk score	139 (113–167)	149 (125–170)	131 (103–160)	<0.0001
CRUSADE risk score	27 (15–40)	24 (12–38)	29 (17–40)	0.03
<b>IN-HOSPITAL MANAGEMENT</b>				
Aspirin	488 (97)	222 (99)	266 (96)	0.15
P2Y12 inhibitors	470 (94)	219 (98)	251 (91)	0.003
Clopidogrel	230 (46)	89 (40)	141 (51)	0.001
Prasugrel	92 (18)	78 (35)	14 (5)	<0.0001
Ticagrelor	148 (29)	52 (23)	96 (35)	0.001
Anti-GPIIb/IIIa	120 (25)	91 (41)	29 (11)	<0.0001
UFH	212 (42)	112 (50)	100 (36)	<0.0001
LMWH	47 (9)	6 (3)	41 (15)	<0.0001
Fondaparinux	100 (20)	9 (4)	91 (33)	<0.0001
Bivalirudin	105 (21)	87 (39)	18 (7)	<0.0001
Coronary angiography	477 (95)	222 (99)	255 (92)	0.001
Multivessel disease	281 (59)	125 (56)	156 (61)	0.30
PCI	356 (75)	201 (90)	155 (61)	<0.0001
IABP	7 (1.4)	6 (2.7)	1 (0.4)	0.03
CABG	31 (6)	7 (3)	24 (9)	0.01
CABG, coronary artery by-pass grafting; eGFR, estimated glomerular filtration rate (MDRD formula); EF, left ventricular ejection fraction; IABP, intra-aortic balloon pump; LMWH, low molecular weight heparin; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin.				

**Table 2.** Clinical characteristics of patients according to P2Y12 inhibitor therapy prescribed. Values are presented as median (interquartile range) or *n* (%).

	Clopidogrel <i>n</i> = 230	Prasugrel/Ticagrelor <i>n</i> = 240	<i>p</i> value
Age (years)	75 (65–81)	61 (53–70)	<0.0001
Age ≥ 75 years	122 (53)	27 (11)	<0.0001
Female	86 (37)	62 (26)	0.007
Diabetes mellitus	71 (31)	51 (21)	0.02
STEMI	89 (39)	130 (54)	0.001
NSTE-ACS	141 (61)	110 (46)	0.001
eGFR < 60 ml/min/m <sup>2</sup>	78 (34)	34 (14)	<0.0001
Anemia	53 (23)	23 (10)	<0.0001
EF (%)	53 (41–58)	55 (48–59)	0.001
Killip class ≥ 2	43 (19)	23 (10)	0.005
Atrial fibrillation	38 (16)	19 (8)	0.005
Acute pulmonary edema	10 (4.3)	4 (1.7)	0.10
Cardiogenic shock	7 (3)	4 (1.7)	0.37
Cardiac arrest	2 (1)	9 (4)	0.06
GRACE risk score	150 (126–177)	125 (103–150)	<0.0001
CRUSADE risk score	35 (23–44)	19 (10–30)	<0.0001
Coronary angiography	218 (95)	236 (98)	0.04
Multivessel disease	146 (67)	121 (51)	0.001
PCI	153 (70)	196 (83)	0.001
IABP	5 (2.2)	2 (0.8)	0.27

eGFR, estimated glomerular filtration rate (MDRD formula); EF, left ventricular ejection fraction; IABP, intra-aortic balloon pump; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

presence of anemia and a Killip class at admission ≥ 2 were independently associated with mortality (Figure 2), while only a moderate or higher risk CRUSADE value was independently associated with overall bleedings.

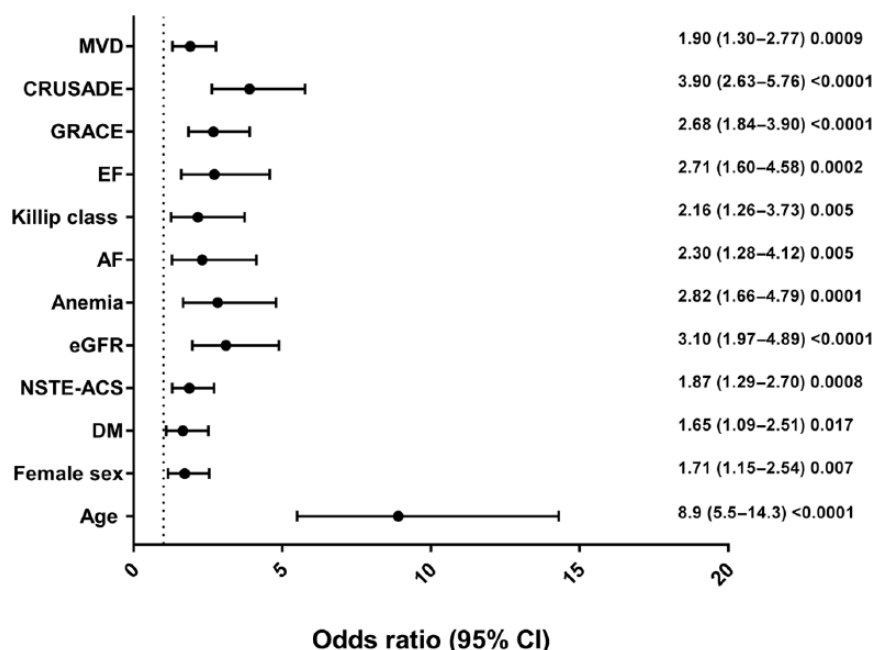
## Discussion

The main results of the present study can be summarized as follows: (i) clopidogrel has been the most frequently used second antiplatelet agent, accounting for nearly half of the prescriptions in the overall population; (ii) clinical variables associated with its use identify patients at higher risk for adverse events; and (iii) this is probably the reason for the higher in-hospital mortality observed in clopidogrel-treated patients.

Although the last European Society of Cardiology (ESC) and ACC/AHA Guidelines for

the management of patients with STEMI and NSTE-ACS<sup>17–20</sup> recommend prasugrel and ticagrelor over clopidogrel as the first choice drugs for double platelet inhibition according to the results of the TRITON-TIMI 38 and of the PLATelet inhibition and patient Outcomes (PLATO) trials showing the superiority of the two new P2Y12 inhibitors in reducing MACE in ACS patients,<sup>9,10</sup> clopidogrel is still widely used in the clinical practice, as highlighted by several international registries.<sup>11,21–26</sup>

In our study clopidogrel was used in 46% of the overall population, and in particular in 40% of STEMI patients and in 51% of NSTE-ACS patients. When compared with previous studies, our prescription rate of clopidogrel in NSTE-ACS patients is similar to that observed in the AMIS-PLUS<sup>21</sup> and in the SCAAR<sup>22</sup> registries. Considering STEMI patients in AMIS-PLUS,<sup>21</sup> SCAAR<sup>22</sup> and MULTIPRAC<sup>23</sup> registries,



**Figure 1.** Clinical characteristics associated with clopidogrel prescription on univariable logistic regression analysis.

Age, age  $\geq$  75 years; AF, atrial fibrillation; CI, confidence interval; CRUSADE, CRUSADE risk score  $>$  30; DM, diabetes mellitus; EF, left ventricular ejection fraction  $\leq$  40%; eGFR, estimated glomerular filtration rate (MDRD formula)  $<$  60 ml/min/m<sup>2</sup>; GRACE, GRACE risk score  $>$  140; Killip class, Killip class  $\geq$  2; MVD, multivessel coronary disease; NSTE-ACS, non-ST-elevation acute coronary syndrome.

**Table 3.** In-hospital adverse events according to P2Y12 inhibitor therapy prescribed. Values are presented as *n* (%).

	Clopidogrel <i>n</i> = 230	Prasugrel/Ticagrelor <i>n</i> = 240	<i>p</i> value
ReMI/UPR	9 (4)	11 (5)	0.82
Overall bleedings	20 (8.7)	10 (4.2)	0.06
BARC 3 bleedings	6 (2.6)	5 (2.1)	0.76
Death	11 (4.8)	1 (0.4)	0.002

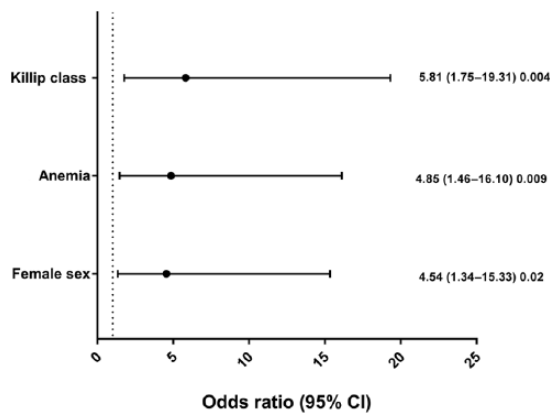
BARC, Bleeding Academic Research Consortium; ReMI, myocardial infarction/re-infarction; UPR, urgent percutaneous revascularization.

however, where clopidogrel was the first choice second antiplatelet agent in 47.8%, 51.3% and 54.4%, our clopidogrel use appears to be lower (40%), with a high new P2Y12 inhibitors prescription rate (58%), in particular of prasugrel (35%). These data, in a similar way as the results of the GReek AntiPlatelet rEgistry (GRAPE) registry,<sup>26</sup> seem to suggest a trend toward a more adherent application of international guideline indications.

Besides the still wide prescription of clopidogrel, these registries highlight the patients' clinical characteristics associated with clopidogrel

utilization in daily clinical practice. In particular, NSTE-ACS diagnosis and age appear to be two important factors favoring clopidogrel prescription.<sup>11,21,22,24–26</sup> This probably reflects the special warnings for prasugrel utilization in elderly patients<sup>9</sup> and the less definite results obtained by its use in NSTE-ACS population<sup>9,27</sup> and the reluctance of ticagrelor utilization in the aged patients because of the higher bleeding risk in this population, despite the favorable results obtained in the elderly substudy of the PLATO trial.<sup>28</sup> According to the aforementioned observations, in our study both advanced age and NSTE-ACS diagnosis were associated with clopidogrel





**Figure 2.** Clinical characteristics independently associated with in-hospital death on multivariable stepwise logistic regression analysis. CI, confidence interval; Killip class, Killip class  $\geq 2$ .

utilization. Patients taking clopidogrel had a median age of 75 years and more than half of them had an age  $\geq 75$  years *versus* only 11% of those taking the new P2Y12 inhibitors. Moreover, at the univariable logistic regression analysis, other clopidogrel use predictors emerged in our study, such as female sex, diabetes mellitus, chronic renal impairment, atrial fibrillation, anemia, worse Killip class and left ventricular function and coronary multivessel disease. In essence, our clopidogrel-treated patients represent a globally higher risk population, both regarding ischemic and bleeding events, as highlighted by the significantly higher values of GRACE and CRUSADE risk scores associated with clopidogrel prescription. This means that in daily practice we face the clinical paradox that patients at higher risk of MACE are treated with the less efficacious P2Y12 inhibitor.<sup>24</sup> On the other hand, since baseline clinical characteristics contribute to the risk of MACE, the outcome data related to the various P2Y12 inhibitors may be confounded in this setting. In this regard, interesting observations can be drawn from the results of the Platelet Inhibition Registry in ACS Evaluation Study (PIRAEUS),<sup>12,13</sup> that aimed to integrate the wide array of data generated by individual registries on the efficacy and safety of P2Y12 inhibitors in ACS. In summary, the various observational studies showed the superiority of both prasugrel and ticagrelor over clopidogrel in terms of MACE and mortality reduction, while more difficult was the comparison regarding bleeding events, because of the different bleeding definitions used in the various registries. At most, a trend toward more

bleedings in clopidogrel-treated patients was observed. In contrast to these data, however, two other observational registries<sup>24,25</sup> did not show any beneficial effect of prasugrel or ticagrelor over clopidogrel regarding MACE and in-hospital or long-term mortality.

In our study, overall in-hospital mortality was 2.6% and overall bleedings were 6.4%. In accordance with the most of registries, we observed a significantly higher in-hospital mortality in clopidogrel-treated patients (4.8%) than in patients treated with prasugrel or ticagrelor (0.4%), while no significant differences were found regarding recurrent ischemic events or urgent revascularization. Finally, a no significant trend toward a higher incidence of overall bleedings in clopidogrel cohort patients was present.

In order to better understand the real relationship between clopidogrel utilization and in-hospital mortality observed in our population, we performed multivariable logistic regression analysis, including along with clopidogrel prescription all the clinical variable associated with its utilization. What we obtained is that clopidogrel is not independently associated with in-hospital mortality, but only female sex, a high Killip class and anemia at admission are independently associated with it. Moreover, as far as bleeding events are concerned, only an at least moderate CRUSADE score value was independently associated with overall bleeding events, confirming the predictive role of this risk model.

These data indicate that in the daily clinical practice a safety-oriented approach prevails when treating patients at high risk because of advanced age and several comorbidities and that the baseline clinical characteristics represent the main negative prognostic factor.

The present study has some limitations. The first one is the relatively limited sample size and the consequent small number of events that may influence the statistic results. A second limitation is that this is a single-institution experience and this might reduce the generalizability of our findings to other populations. However, we think that our population, although relatively small, is a well-balanced mix of ACS patients. As a matter of fact, it represents a contemporary population of ACS, being almost equally subdivided in STEMI and NSTEMI-ACS patients managed according to current clinical practice.

### Conclusion

In our unselected ACS patient population, clopidogrel has been widely prescribed and patients treated with clopidogrel showed a higher in-hospital mortality and a trend toward more bleeding events. However, clinical variables associated with its use identify a population at high risk for adverse events and clopidogrel per se does not seem independently associated with higher in-hospital mortality.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

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