

ORIGINAL ARTICLE

Is There Safety in the Use of Clopidogrel Loading Dose in Patients Over 75 Years of Age with Acute Coronary Syndrome?

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Abstract

Background: There is limited evidence in the literature regarding the administration of clopidogrel to acute coronary syndrome (ACS) in patients over 75 years of age. Most studies excluded this age group, making the subject controversial due to the increased risk of bleeding in this population.

Objective: This is a retrospective, unicentric, and observational study aimed at assessing whether the administration of clopidogrel loading dose increases bleeding rates in patients over 75 years of age.

Methods: Patients were divided into two groups: group I: 75 mg of clopidogrel; group II: 300-to 600-mg loading dose of clopidogrel. A total of 174 patients (129 in group I and 45 in group II) were included between May 2010 and May 2015. Statistical analysis: The primary outcome was bleeding (major and/or minor). The secondary outcome was combined events (cardiogenic shock, reinfarction, death, stroke and bleeding). The comparison between groups was performed through Q-square and T-test. The multivariate analysis was performed by logistic regression, being considered significant $p < 0.05$.

Results: Comparisons between groups I and II showed differences in the prevalence of diabetes (46.5% vs. 24.4%, $p = 0.01$), arterial hypertension (90.7% vs. 75, $p = 0.01$), dyslipidemia (62% vs. 42.2%, $p = 0.021$), ST segment elevation (11.6% vs. 26.6%, $p = 0.016$) and coronary intervention percutaneous (16.5% vs. 62.2%, $p < 0.0001$), respectively. In the multivariate analysis, significant differences were observed between groups I and II in relation to the occurrence of bleeding (8.5% vs. 20%, OR = 0.173, 95% CI: 0.049 - 0.614, $p = 0.007$).

Conclusion: The use of a loading dose of clopidogrel (≥ 300 mg) in the population over 75 years of age is associated with higher bleeding rates. (Int J Cardiovasc Sci. 2019;32(5):449-456)

Keywords: Platelet Aggregation Inhibitors/therapeutic use; Acute Coronary Syndrome/complications; Aged; Hemorrhage; Treatment Outcome.

Introduction

Among the elderly population, only 40% of patients over 75 years of age receive reperfusion therapy in the United States.¹ Consistent with these numbers, a recent study in England found that older patients were incrementally less likely to receive invasive and medical therapy.² Current guidelines do not suggest any age-related limitations of medical or invasive therapy, stating that percutaneous coronary intervention (PCI)

in acute coronary syndrome (ACS) is beneficial for elderly patients.³⁻⁸

However, there is little evidence in the literature concerning the use of loading dose of clopidogrel in patients aged over 75 years with ACS. Most randomized studies have excluded this age group, and hence there is limited data available, which makes the subject controversial, due to increased bleeding risk in this population.¹ The description of these comparative data in Brazilian registries has not yet been documented.

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Thus, this study was developed with the purpose of assessing whether the administration of a 300 mg or 600 mg loading dose of clopidogrel increases in-hospital bleeding rates in patients over 75 years of age.

Methods

Study population

This is a retrospective, unicentric and observational study. We included 174 (12.9% of total) individuals with ACS aged > 75 years, admitted to the emergency sector between May 2010 and May 2015. The patients were divided into two groups: group I: 75 mg loading dose of clopidogrel (N = 129); group II: 300 to 600 mg loading dose of clopidogrel (N = 45). There were no additional exclusion criteria.

All patients who met the criteria established by the latest guidelines of the Brazilian Society of Cardiology and the American Heart Association were considered to have had ACS.^{3,4} ACS with no ST segment elevation was defined as the presence of chest pain associated with electrocardiographic alterations or rise/drop of troponin upon admission, or, in the absence of these factors, a clinical picture and risk factors consistent with unstable angina (chest pain when resting or with minimal effort, severe pain, or with an improving pattern). Major bleeding was defined by the score of BARC⁹ types 3 and 5, and minor bleeding by types 1 and 2. Reinfarction was considered in cases of recurrence of chest pain linked to the new troponin elevation. Ischemic cerebrovascular accident (iCVA) was considered when the patient displayed new focal motor neurological deficit confirmed through cranial computerized tomography.

All patients underwent coronary angiography within the first 24h after admission. All percutaneous coronary interventions (PCI) were performed with conventional stents.

The following data were obtained: age, sex, presence of diabetes mellitus, systemic arterial hypertension, smoking, dyslipidemia, family history of early coronary disease, heart failure, previous coronary artery disease (acute myocardial infarction, angioplasty or previous surgical myocardial revascularization), hemoglobin, creatinine, troponin peak, left ventricular ejection fraction, systolic blood pressure, medications used within the first 24 hours of admission and the coronary treatment adopted.

This study was submitted and approved by the Research Ethics Committee. The written informed

consent form was signed by all patients included in the study.

Statistical analysis

The primary in-hospital outcome was bleeding. The secondary outcome was combined events (cardiogenic shock, reinfarction, death, stroke and bleeding). The descriptive analysis was done using means and standard deviation when parametric tests were used and median and interquartile intervals in non-parametric tests. The comparison between groups was made through Q-square for the categorical variables. For continuous variables, when the Komolgorov-Smirnov normality test showed normal distribution, the variables were calculated using the T-test, considering as significant $p < 0.05$. When the distribution did not follow the normality standard, we used the Mann-Whitney U test. An additional univariate analysis was conducted through Q-square test, comparing mortality between patients who bled versus those who did not present the outcome and also comparing major bleeding rates between groups I and II. The multivariate analysis was performed through logistic regression only when a significant difference was found between the groups in any of the outcomes assessed, and considering as significant $p < 0.05$. All baseline characteristics presented by Table 1 were considered as variables in the analysis.

All calculations were performed using the SPSS Statistics Base v10.0 software.

Results

The mean age was 80.2 years in group I versus 80.5 years in group II ($p = 0.728$). The baseline characteristics of the population studied are presented by Table 1.

In relation to the treatment, the performance of PCI was observed in 16.5% in group I and 62.2% in group II ($p < 0.0001$). Surgical myocardial revascularization was performed in 9.3% of group I versus 4.4% of group II ($p = 0.302$).

In the univariate and multivariate analysis, significant differences were observed between groups I and II in relation to bleeding rates (8.5% vs. 20%, OR = 0.173; 95% CI: 0.049 – 0.614, $p = 0.007$), respectively. The results of the univariate and multivariate analysis, comparing different in-hospital outcomes between the groups, are presented by Table 2.

Table 1 - Baseline clinical characteristics of elderly ACS patients who received 75 mg clopidogrel (group I) versus 300 - 600 mg clopidogrel (group II) in the sample studied

	Group I	Group II	p
Age (mean)	80.2 + 4.3	80.5 + 4.7	0.728 π
Diabetes Mellitus (%)	46.5	24.4	0.01#
SAH (%)	90.7	75.6	0.01#
Smoking (%)	30.2	17.8	0.105#
Positive FH for CAD (%)	8.5	6.7	0.693#
Dislipidemia (%)	62	42.2	0.021#
CI (%)	7.9	4.4	0.451#
Previous CVA (%)	10.1	6.7	0.495#
Previous AMI (%)	37.2	42.2	0.552#
Previous SMR (%)	15.5	22.2	0.304#
Previous TCA (%)	26.4	35.6	0.24#
Hb (mg/dL) (mean)	14.6 + 1.9	13.2 + 1.7	< 0.001 π
Troponin peak (mean) (ng/dL)	11.8 + 5.9	8.0 + 7.2	< 0.001 π
Cr (mg/dL) (mean)	1.3 + 0.5	1.5 + 0.4	< 0.0001 π
SBP (mmHg) (mean)	134.2 + 29.4	133.0 + 27.2	0.104 π
LVEF (%) (mean)	52.3 + 19.9	51.8 + 18.7	0.09*
STEMI (%)	11.6	26.7	0.016#
ASA (%)	98.4	100	0.401#
Beta-blockers (%)	51.2	40	0.197#
GPI IIb/IIIa (%)	5.4	0	0.111#
Enoxaparin (%)	74.4	71.1	0.665#
Fibrinolytic (%)	2.3	0	0.302#
Statins (%)	82.2	95.6	0.088#
ACEi (%)	49.6	53.3	0.667#

SBP: systolic blood pressure; SAH: systemic arterial hypertension; FH: family history; CAD: coronary artery disease; HF: heart failure; CVA: cerebral vascular accident; AMI: acute myocardial infarction; SMR: surgical myocardial revascularization; TCA: coronary angioplasty; Hb: hemoglobin; Cr: creatinine; LVEF: left ventricular ejection fraction; GPI: glycoprotein inhibitor; ACEi: Angiotensin-Converting Enzyme Inhibitor. #: Q-square test; *: Student's t-test; π : Mann-Whitney U test.

As for the incidence of hemorrhagic complications, the most frequent was hemorrhagic stroke (50% of cases), followed by femoral artery puncture (35%), epistaxis

(10%) and hemarthrosis (5%). Major bleeding occurred in 45.5% of patients in group I and 44.4% in group II ($p = 0.672$). Mortality rate among patients who had any type of bleeding versus those who had no bleeding was 25% vs. 4.5% ($p < 0.0001$). Types of bleeding per group can be observed in Figure 1. The types of vascular accesses were also similar between the groups, with radial access being used in 48% of patients in group I and 51% in group II ($p = 0.347$).

Discussion

This study showed important data reproduced in the Brazilian population on a controversial issue in the literature. We reported higher reperfusion rates (especially percutaneous) and ACS with ST elevation in patients in group II, in a significant manner. In relation to bleeding, significant differences were observed, with a higher incidence in patients who received clopidogrel (300-mg to 600-mg loading dose). Furthermore, hemorrhagic stroke was the most prevalent bleeding disorder and the occurrence of any bleeding (major or minor) had an impact on higher in-hospital mortality rates. Nevertheless, in the comparison between groups I and II there were no differences regarding mortality and combined events.

The current guidelines recommend the use of full treatment and loading dose of clopidogrel in patients aged over 75 years, without almost any distinction when compared to younger patients. The current guidelines of the American Heart Association, the European Society of Cardiology or the Brazilian Society of Cardiology,³⁻⁸ suggest that the 600-mg loading dose is preferable in all patients undergoing PCI. The only exception, which contemplates the elderly, refers to patients aged over 75 years undergoing fibrinolytic therapy, for whom only the dose of 75 mg clopidogrel is recommended, with no additional loading dose.³⁻⁸ However, until 2015, in Brazil, the guidelines recommended that only the 75-mg clopidogrel dose should be administered to all patients aged over 75 years, with no loading dose.¹⁰ This recent change in the guidelines allowed for a retrospective analysis of data and the assessment of the safety of the use of clopidogrel in older patients undergoing invasive procedures, following the previous recommendation in contrast with the new recommendation, since fibrinolytics were used in less than 2% of cases.

The most cautious recommendation concerning the elderly, which prevailed until 2015, came primarily from

Table 2 - A. Results of the univariate analysis comparing different in-hospital outcomes in elderly ACS patients who received 75 mg clopidogrel (group I) versus 300 - 600 mg clopidogrel (group II); B. Results of the multivariate analysis comparing different bleeding among elderly ACS patients who received 75 mg clopidogrel (group I) versus 300 – 600 mg clopidogrel (group II)

A					
	Group I	Group II	p		
Reinfarction	2.1%	0.0%	0.497		
Cardiogenic shock	8.2%	0.0%	0.163		
Bleeding	8.5%	20%	0.038		
iCVA	2.1%	4.5%	0.502		
Mortality	8.5%	6.7%	0.054		
Combined events	29.4%	31.2%	0.105		

B					
	Group I	Group II	OR	CI 95%	p
Bleedings (%)	8.5	20.0	0.173	0.049 – 0.614	0.007

iCVA: ischemic cerebrovascular accident; OR: Odds ratio; CI: confidence interval.

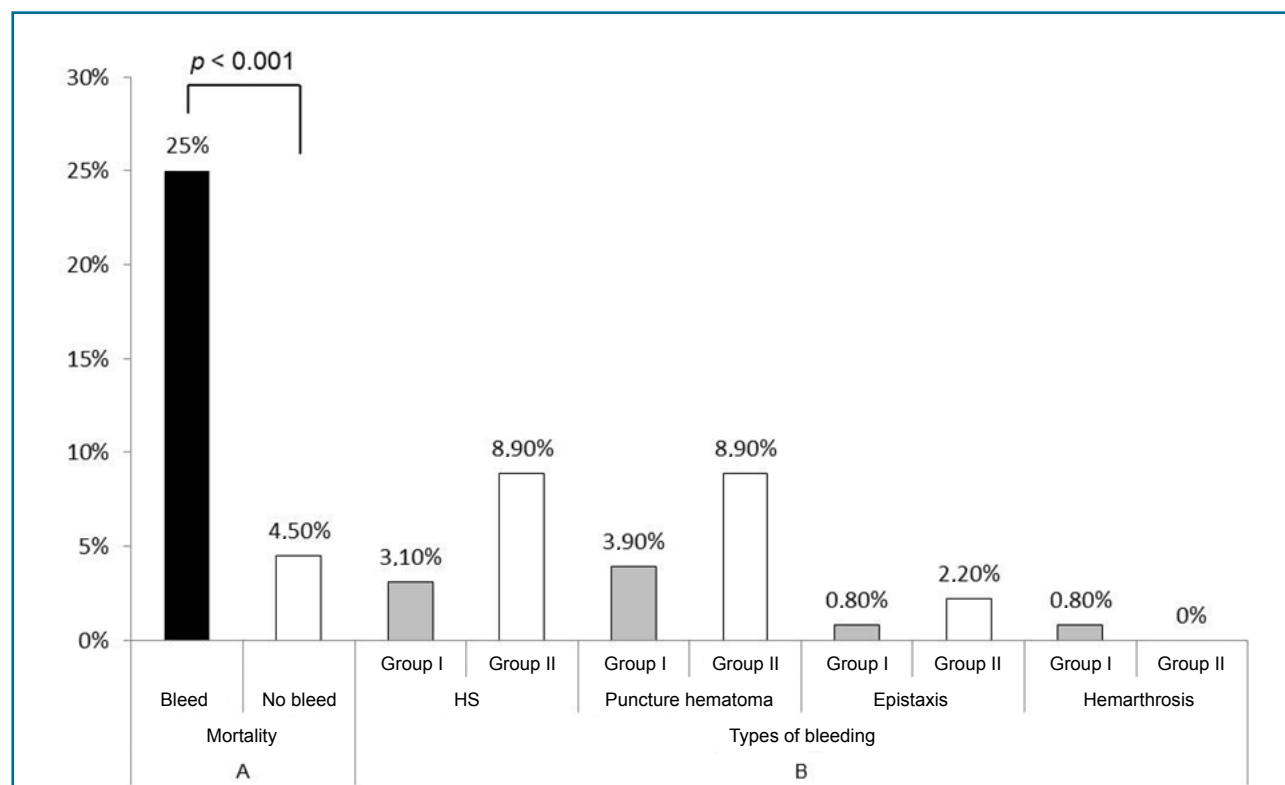


Figure 1 - A. Univariate analysis comparing mortality rates between patients who bled versus those who did not; B. Description of the types of bleeding between patients receiving 75 mg clopidogrel (group I) versus 300 - 600 mg clopidogrel (group II)
 HS: hemorrhagic stroke.

the COMMIT/CCS-2 studies, carried out exclusively in China, which included more than 40,000 patients with acute myocardial infarction (AMI). The patients were randomly allocated clopidogrel 75 mg daily (no loading dose) or matching placebo. Treatment with clopidogrel produced a 9% reduction in the co-primary outcomes: death, AMI or stroke. Safety outcomes (cerebral, transfusion and fatal bleeds) did not differ significantly among the groups (clopidogrel 0.58% versus placebo 0.55%; $p = 0.59$). Although fibrinolytics were predominantly used in this study, there was an extrapolation and the recommendation was directed to all ACS-related cases.¹¹

However, concerns with stent thrombosis and the use of clopidogrel started to bring new evidence into the discussion. It has been shown that there is mainly genetic resistance to clopidogrel, mechanisms that limit its absorption and lead to delayed metabolism. Hence, higher loading doses have been tested, especially in patients undergoing early PCI and who need the drug bioavailability in a short period of time.¹²⁻²⁶ The greatest study was the CURRENTOASIS 7 trial, which included 25,086 patients with ACS and intended PCI (29% with STE-ACS). Patients were assigned to double-dose (600 mg on day 1, 150 mg on days 2-7, then 75 mg daily) versus standard-dose (300 mg on day 1 then 75 mg daily) clopidogrel. There was a significant decrease in primary outcome rates within a 30-day follow-up, especially due to reduced non-fatal infarction and stent thrombosis rates. However, the mean age of the patients included was only 61 years and major bleeding was more common in the group receiving the double-dose clopidogrel (1.5% vs. 1.1%, $p = 0.014$).¹² Since the net benefit was greater, high-dose clopidogrel started to be indicated and modifications were made in the guidelines, but specific subgroups, with a high risk of bleeding, were not taken into account, because they were not included in these studies.

Most studies of PCI in ACS patients normally exclude the elderly. When all clinical trials are considered, only about 9% of patients are over 75 years of age and the mean age ranges between 55 and 65 years. Nevertheless, in real clinical practice, about 35% of patients belong to this age group, whose baseline clinical characteristics are completely distinct from the rest of the population.^{1,24,27} A study conducted in 2011, specifically in patients aged 75 years or older, compared the platelet reactivity and clopidogrel

response between patients aged > 75 years and < 75 years undergoing PCI for non-ST-segment elevation ACS. A total of 689 patients were enrolled and all of them received a loading dose of 600 mg clopidogrel followed by 150 mg/day. Post-treatment platelet reactivity was higher in patients older than 75 years of age than in younger patients. However, the pharmacologic response to clopidogrel was not impaired in patients > 75 years, not showing a relationship between platelet reactivity and response to the drug.²⁸ Besides, the group of patients aged over 75 years had higher bleeding rates (12% vs. 8%, $p = 0.03$) compared to younger patients.²⁸

Lin et al.,²⁹ also carried out a study on the effect of antiplatelet therapy on elderly patients. They tested standard versus low-dose tirofiban in elderly patients (> 80 years) who underwent PCI. The rate of combined ischemic events was not significantly different at 7 days, 30 days and 6 months. Bleeding events were significantly higher in the standard-dose group (10.4% vs. 0.0%, $p = 0.03$). The authors concluded that, in very elderly high-risk patients undergoing PCI, low-dose tirofiban offered the same level of protection, with less associated bleeding.²⁹

Data from a German STEMI registry compared patients aged under 75 years (group I), between 75 and 85 years (group II) and over 85 years (group III). Bleeding was observed more often with increasing age (group I: 5.4% vs. group 2: 11.0% vs. group 3: 19.6%, $p < 0.0001$). Similarly and directly related, mortality rates during in-hospital and long-term course increased with increasing age.³⁰ Classically, bleeding is associated with a fourfold increased risk of death, a five-fold increased risk of reinfarction and a threefold increased risk of stroke. The need for suspension of antiplatelet/anticoagulant drugs increases the risk of ischemic events, especially stent thrombosis.³¹

Similarly, the CRUSADE registry assessed bleeding rates in 32,895 NSTEMI-ACS patients aged over 65 years and their impact on mortality rates among this group. About 11.9% of the patients had major bleeding during hospital stay. Mortality rates were higher among those patients who had major bleeding compared to those with no bleeding, both within 30 days (HR = 1.33; 95% CI: 1.18 – 1.51), 1 year (HR = 1.19; 95% CI: 1.10 – 1.29) and also within 3 years (1.14; 95% CI: 0.99 – 1.31).³²

Thus, the greatest concern in relation to patients aged over 75 years is to find a balance between the

appropriate pharmacological invasive treatment and the risk of bleeding and complications inherent to this age group. This study presents a change in bleeding rates that has a total correlation with the stance adopted by the guidelines. In spite of a greater number of ACS patients with ST-segment elevation and those undergoing PCI in the group who received clopidogrel loading dose, this study did not find any differences between the groups in relation to medications, performance of invasive procedures, number of radial vascular accesses and possible confounding variables adjusted for in the multivariate analysis. Still, bleeding remained as the independent and differential factor between the groups. Due to lack of strong evidence in this population, perhaps non-ST-segment ACS patients undergoing PCI in a range greater than 4 to 6 hours should receive doses less than 600 mg clopidogrel. Furthermore, it would be interesting and necessary to develop a randomized clinical trial to establish the best clinical therapy for the subgroup of patients aged over 75 years. Finally, the model of events prediction is hardly applicable to this population. The ideal would be to have a score which took into account frailty, dementia, level of dependence and other intrinsic characteristics of the elderly.^{1,33,34}

Limitations

This is a retrospective study, with limited number of cases and a much greater number of patients in group I, compared to group II, since medication doses were administered according to the instructions of the doctor responsible for the case. Therefore, some more specific comparisons were not performed. Analysis of mortality and reinfarction cannot be inferred in this study. Nevertheless, we believe this study to be relevant, since guidelines are discordant and there is few data available in the literature on this issue.

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Conclusion

The use of a loading dose of clopidogrel (≥ 300 mg) in the population over 75 years of age is associated with higher bleeding rates.

Author contributions

Conception and design of the research: Alexandre Soeiro, Guilherme Casale; Acquisition of data: Alexandre Soeiro, Guilherme Casale, Maria Antonieta A. A. M. Lopes, Lucas Colombo Godoy; Analysis and interpretation of the data: Aline Siqueira Bossa; Statistical analysis: Aline Siqueira Bossa; Writing of the manuscript: Alexandre Soeiro; Critical revision of the manuscript for intellectual content: Bruno Biselli, Tatiana C. A T. Leal, Maria Carolina F. A. Soeiro; Supervision / as the major investigator: Carlos V Serrano Jr., Múcio T. Oliveira Jr.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAPPesq under the protocol number 881.656. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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