Causality Analysis of the Relationship Between Bleeding and Lethality in Acute Coronary Syndromes

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Abstract

Background: **Hemorrhagic events in Acute Coronary Syndromes (ACS) have been independently associated with death in international multicenter registries. However, that association has not been tested in Brazil and the true causal relationship between bleeding and death has not been completely shown.**

Objective: **To test the following hypotheses: (1) major bleeding is an independent predictor of in-hospital death in ACS; (2) the relationship between those two endpoints is causal.**

Methods: **This study included patients meeting predefined criteria of unstable angina, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. Major bleeding during hospitalization was defined according to the Bleeding Academic Research Consortium (types 3 or 5). Logistic regression and analysis of the sequence of events were used to assess the association between bleeding and death.**

Results: **Of the 455 patients studied, 29 experienced major bleeding (6.4%; 95% CI = 4.3-9.0%). They had in-hospital mortality of 21%, as compared with 5.6% of those not experiencing bleeding (RR = 4.0; 95% CI = 1.8-9.1; P = 0.001). After adjusting for the propensity score, major bleeding remained as a predictor of in-hospital death (OR = 3.34; 95% CI = 1.2-9.5; P = 0.02). Of the 29 patients who experienced bleeding, six died. However, the detailed analysis of the sequence of events showed causal relationship only in one case.**

Conclusion: **(1) Major bleeding is an independent predictor of in-hospital death in ACS; (2) the role of bleeding as a risk marker overcomes that as a risk factor for death. This conclusion should be seen as a hypothesis generator to be confirmed by larger-sample studies. (Arq Bras Cardiol 2012;98(6):488-496)**

Keywords: **Acute coronary syndrome; angina, unstable; myocardial infarction; hemorrhage/complications; hemorrhage/prevention & control; hospitalization.**

Introduction

Individuals developing unstable angina or myocardial infarction are at high risk for ischemic complications during the acute phase[1,2]. Thus, aggressive pharmacological and interventional therapies have been early adopted to minimize the likelihood of recurrent endpoints, such as refractory angina, infarction or cardiovascular death[3,4]. However, those same therapies increase the likelihood of hemorrhagic events during hospitalization[5], which, in turn, increase the risk of ischemic events[6]. Thus a paradox emerges, in which treatments aimed at reducing the cardiovascular risk of patients with acute coronary syndromes (ACS) might increase their risk through hemorrhagic complications.

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That paradox has been supported by scientific evidence. Large prospective registries have consistently shown that individuals experiencing bleeding during hospitalization have a higher probability of death[6-11]. A causal association is believed to exist between bleeding and in-hospital lethality in ACS, because there is plausibility in the statement that the hemodynamic instability due to bleeding, anemia and need for suspending antithrombotic agents causes myocardial ischemia. This possible causal association is reinforced by the independent predictive role played by hemorrhagic events in multivariate models assessing the cardiovascular death endpoint in that clinical circumstance[6-12]. On the other hand, causality is defined by not only plausibility or independent association, and the large prospective registries have not described in details the sequence of events leading to death in those individuals.

The present study has two objectives: first, to test the independent prognostic value of major hemorrhagic events during the acute phase of coronary syndromes. This is the first attempt to reproduce the data of the international literature in a Brazilian registry. Second, to analyze individually the sequence of events leading some patients experiencing

bleeding to death, aiming at confirming the causal relationship between those two endpoints. This is the first attempt to understand the true causal nature of that relationship.

The analysis used the Prospective Registry of Acute Coronary Syndromes (RESCA), including 455 patients meeting strict selection criteria, in which major hemorrhagic events, recurrent ischemic events and death were registered during hospital follow-up. In that analysis, the hemorrhagic events were classified according to the recent *Bleeding Academic Research Consortium (BARC)*[13].

Methods

Selection of the population

The study sample was recruited from two tertiary hospitals, which are referral centers of cardiology and have similar characteristics regarding health care and patients' profile. Patients consecutively admitted to the Coronary Unit diagnosed with ACS were screened to enter the study, from August 2007 to September 2009 in the first hospital, and from May to December 2010 in the second one.

Acute coronary syndrome without ST-segment elevation has been defined as a chest discomfort in the previous 48 hours, associated with at least one of the following characteristics: 1) positive marker of myocardial necrosis, defined by troponin T ≥ 0.01 ug/L or troponin I ≥ 0.034 μg/L, corresponding to values over the 99th percentile of the reference population[14]; 2) ischemic electrocardiographic changes, consisting in T wave inversion (≥ 0.1 mV) or transient depression of the ST segment (≥ 0.05 mV); 3) and previously documented coronary artery disease, defined as a history of myocardial infarction or previous angiography showing coronary obstruction ≥ 50%.

ST-segment elevation acute myocardial infarction (STEMI) has been defined as chest discomfort in the preceding 48 hours, associated with ST-segment elevation ≥ 1 mm in two contiguous leads and elevated serum markers of myocardial necrosis, as previously described.

Patients meeting the inclusion criteria and providing written informed consent were included in the study. The study protocol was approved by the Committee on Ethics and Research of the hospital.

Definition of in-hospital bleeding

For the purpose of data analysis, major bleedings were considered, defined according to the *BARC*[13] as follows: (1) type 3a: 3% to 5 g% hemoglobin drop or need for blood transfusion; (2) type 3b: hemoglobin drop ≥ 5 g%, cardiac tamponade, bleeding requiring surgical intervention or intravenous vasoactive agents; (3) type 3c: intracranial hemorrhage or intraocular bleeding; (4) type 5: fatal bleeding, that is, that with a clear causal relationship to subsequent death. That relationship can be direct (for example, death due to hemorrhagic shock) or indirect (infarction caused by bleeding, evolving to heart failure and death). Minor bleedings (type 1 or 2) or those resulting from heart surgery (type 4) were not considered in this analysis. In addition to this definition, the hemorrhagic events were classified according to the bleeding site. Although the *BARC* has been published recently, all data necessary for that classification were defined *a priori*, assuring the prospective character of data collection.

In-hospital death was prospectively recorded and divided into two groups as follows: bleeding-related and non-bleeding-related death. Non-fatal ischemic events were defined as infarction (or reinfarction) or refractory angina. Non-fatal infarction was recorded during hospitalization in the presence of an elevation in troponin levels, which had been negative in the first 24 hours. For patients with infarction on admission, a new peak of CK-MB (> 50% of the previous level and above the normal value) was required for defining reinfarction. The elevation in the markers of necrosis induced by a percutaneous coronary procedure or coronary artery bypass grafting was not recorded as a recurrent event. Refractory angina during hospitalization was defined as recurrent chest pain, at least twice, regardless of the use of nitrates and of the double product control.

Data analysis

The incidence of major bleeding was described as relative frequency and confidence interval with 95% precision (95% CI). The univariate association between bleeding and in-hospital death was described as relative risk and 95% CI. Initially, the clinical characteristics prior to bleeding, antithrombotic therapy and frequency of the percutaneous intervention were compared between those experiencing bleeding and the other patients to identify potential predictors of bleeding ($p \leq 0.10$). Then, those predictors of bleeding were compared between patients who died and those who did not die while hospitalized, and the variables associated with death were identified by use of a p value ≤ 0.10. Thus, the variables simultaneously associated with bleeding and death were selected for a multivariate model, to define a propensity score for bleeding. By using logistic regression and major bleeding as endpoint, the variables with p value < 0.05 in the final model comprised the propensity score. The C-statistics of that score was calculated and described with its confidence interval.

Aiming at assessing the independent association of bleeding and death, a second logistic regression model was used, with in-hospital death as the endpoint variable and bleeding as the predictive variable, adjusted for the propensity score. For the statistical analysis, the SPSS Statistical Software (Version 9.0, SPSS Inc., Chicago, Illinois, USA) was used.

Finally, a qualitative analysis of the causal relationship between bleeding and death, restricted to patients who bled and died, was performed. In that analysis, the sequence of the facts leading to death was carefully detailed, to assess the existence of causal relationship between those two endpoints.

Results

Characteristics of the sample

The sample consisted in 455 patients (54% of the male sex; mean age, 67 ± 13 years), 78% of whom were hospitalized due to ACS without ST-segment elevation, and the others due to STEMI. During hospitalization, coronary angiography was performed in 77% of the patients, percutaneous coronary artery intervention in 37%, and coronary artery bypass grafting in 8%. The sample showed a bleeding score acuity[15] of 16

± 6.8, indicating a 5% higher probability of major bleeding during hospitalization, corresponding to moderate risk. Major bleeding during hospitalization was observed in 29 patients, resulting in a 6.4% incidence (95% CI: 4.3 - 9.0%).

Regarding the major bleedings, those related to the femoral catheter insertion site for coronary angiography (31%) or angioplasty (48%) predominated, corresponding to 79% of the cases. Digestive bleeding (14%) and nasal bleeding (6%) were also observed. According to the *BARC*[13], most bleedings (82%) were classified as type 3a, followed by type 3b (14%), and type 5 (only one fatal case). Considering the patients who bled, 55% received transfusion, 72% showed a hemoglobin drop ≥ 3g%, and only 14% developed hemodynamic instability directly due to bleeding. Only in 17% of the patients, the antithrombotic agents were suspended due to bleeding (Figure 1).

Bleeding and in-hospital death

Patients experiencing major bleeding had an in-hospital mortality of 21%, significantly greater than the 5.6% observed in those without bleeding (Relative Risk = 4.0; 95% CI: 1.8 – 9.1; p = 0.001).

To assess the independent association between bleeding and death, a propensity score for bleeding was developed. Initially, the clinical characteristics and the approaches preceding the bleeding were compared between patients who experienced bleeding and those who did not. Compared with the latter, the former were older, had a higher heart rate, and a higher prevalence of positive troponin and of severe coronary artery disease. Regarding treatment, patients who bled used more frequently glycoprotein (GP) IIb/IIIa inhibitors, and underwent coronary angiography and coronary angioplasty ($p \leq 0.10$ for all patients) (Table 1). Of those variables, age, heart rate, troponin and severe disease were associated with mortality ($p < 0.05$) (Table 2). Thus, those parameters (associated simultaneously with bleeding and death) entered a logistic regression model, bleeding being the endpoint variable. In the final model, age and severe coronary artery disease remained as independent predictors of bleeding (Table 3). That final model was used as a propensity score for bleeding, showing a C-statistics of 0.76 ($p < 0.001$). After adjusting for the propensity score by use of logistic regression, major bleeding remained an independent predictor of death, with Odds Ratio of 3.34 (95% CI: 1.2 – 9.5; p = 0.02) (Table 4).

Analysis of the causal relationship between bleeding and death

The chronology of the events was assessed in the six patients who died after bleeding, to individually analyze the possible causal relationship between those two endpoints (Table 5).

Patient #1, a 73-year-old woman, admitted with non-ST-segment elevation myocardial infarction (NSTEMI), showed a clear causal relationship between bleeding and death. She underwent coronary angiography via the femoral route, which showed no significant coronary artery obstruction. However, hours after the procedure, she developed profuse bleeding through the introducer sheath site, progressing to hemorrhagic shock. A substantial elevation in myocardial necrosis markers was observed, characterizing infarction secondary to shock. The patient did not manage to recover her hemodynamic condition, progressing to refractory shock, followed by death one day after bleeding. Thus, patient #1 is a case of type 5 (fatal) bleeding.

The other five patients could not be classified as type 5 bleeding, that is, no clear causal relationship between bleeding and fatal endpoint could be identified. Patient #2, an 81-year-old man, was admitted with NSTEMI, evolving with refractory angina and cardiogenic shock. He underwent angioplasties of the left main coronary artery, anterior descending artery, and circumflex and right coronary arteries, without improving his hemodynamic condition, and evolving to death after a few days. During the prolonged angioplasty, hemoglobin drop occurred, requiring blood transfusion, and characterizing type 3a bleeding. This patient had already had shock prior to bleeding, and, thus, the hemodynamic instability responsible for his death was not caused by hemorrhage.

Patient #3, a 92-year-old woman, was admitted with NSTEMI, which culminated in refractory angina and acute pulmonary edema, being placed on invasive mechanical ventilation. She progressed with respiratory infection, during which she experienced digestive bleeding, considered a type 3a major bleeding because of the hemoglobin drop. She progressed to septic shock and eventually died. Before the hemorrhage, the patient had already had severe heart failure, her bleeding resulting from the severity of her condition.

Patient #4, a 71-year-old man, underwent thrombolysis during an extensive anterior STEMI, which caused nasal bleeding with no hemodynamic repercussion, characterized as type 3a major bleeding because of the hemoglobin drop. The coronary angiography evidenced diffuse coronary disease, which could be approached through neither angioplasty nor surgery. A few days later, the patient developed cardiogenic shock, probably due to her ventricular function loss consequent to infarction, with no apparent association with the hemorrhagic event.

Patient #5, a 73-year-old woman, was admitted with late STEMI, Killip class I. Her coronary angiography evidenced obstruction of the anterior descending artery, and no angioplasty was performed because of the late character of the presentation. She experienced bleeding during the introducer sheath withdrawal, classified as type 3a, because it required blood transfusion and had no hemodynamic repercussion. However, the patient developed renal failure due to contrast medium, which culminated in dialysis need, and complicated with infection and, eventually, death. Because no hemodynamic instability occurred, her renal failure could not be attributed to bleeding.

Finally, patient #6, a 63-year-old woman, was admitted with STEMI, Killip class I. She underwent late angioplasty of the circumflex artery, evolving to bleeding on the procedure site, need for blood transfusion and hypotension (type 3b bleeding). Hemodynamic stabilization occurred, and elective coronary artery bypass grafting of the anterior descending and right coronary arteries was planned. Death resulted from post-operative complications, not characterizing a causal relationship with the bleeding occurred during the angioplasty.

Thus, of the six patients who bled and died, in only one the death was directly related to the hemorrhagic event.

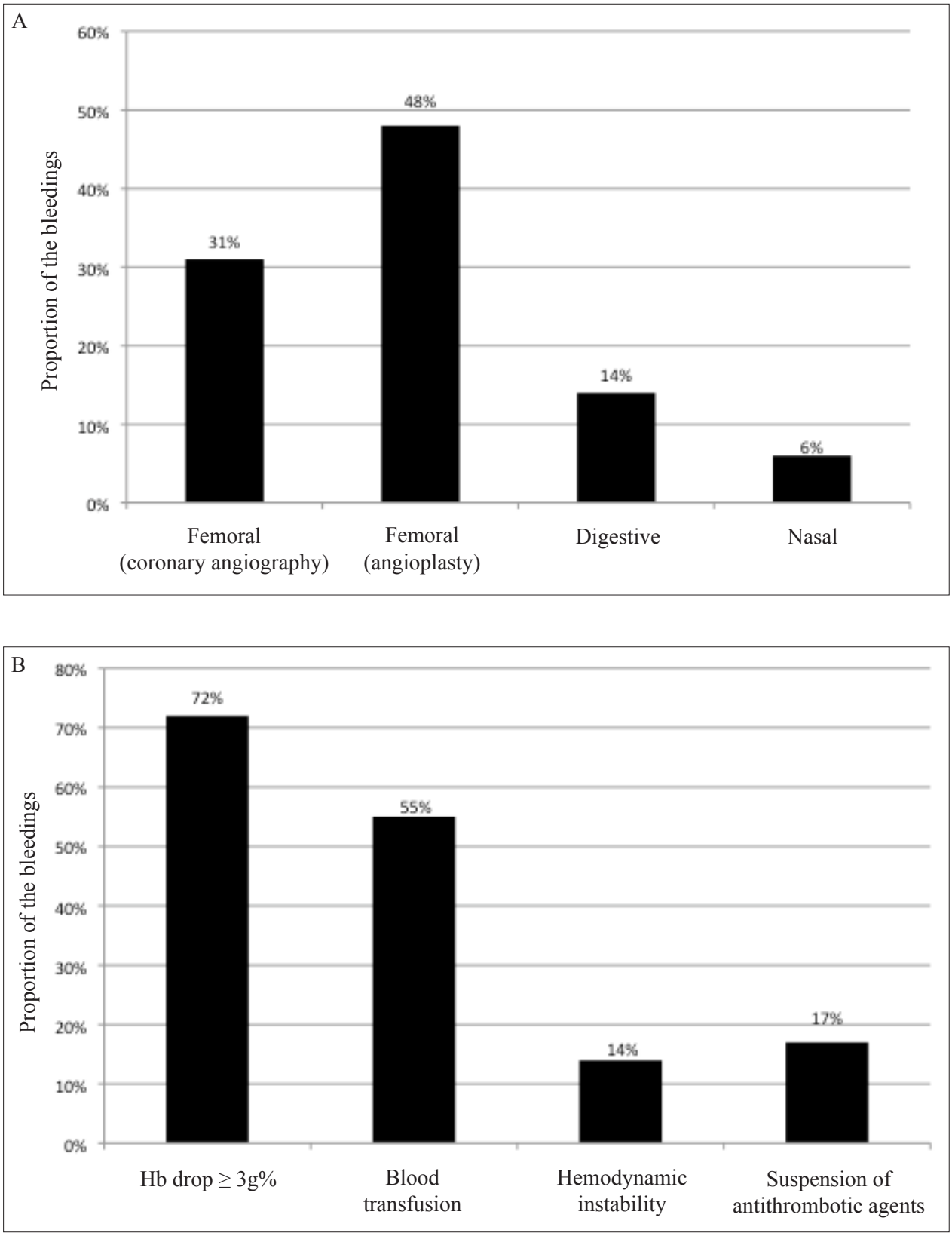

Figure 1 - *Panel A depicts the distribution of the bleeding sites (mutually exclusive options) and shows the predominance of events caused by the percutaneous procedure. Panel B represents the proportion of the different bleeding impacts (non-exclusive options), indicating that the majority has a hemoglobin drop ≥ 3 g%, half requires blood transfusion, while only the minority has hemodynamic instability.*

Table 1 – Association between major bleeding and the clinical characteristics/managements

	Bleeding	No bleeding	p value
Sample size	29	426	
Age (years)	75 ± 11	67 ± 13	0.001
Female sex	13 (45%)	233 (55%)	0.30
STEMI	8 (28%)	92 (22%)	0.45
NSTEMI	21 (72%)	334 (78%)	0.45
Body mass index (kg/m^2)	26 ± 6.6	27 ± 4.8	0.30
Diabetes	13 (45%)	151 (36%)	0.31
Vascular disease	3 (10%)	18 (4.2%)	0.13
Serum creatinine (mg/dL)	1.0 (0.85 – 1.3)	1.0 (0.80 – 1.2)	0.28
Hemoglobin (g/dL)	13 ± 1.5	13 ± 1.8	0.74
Systolic blood pressure (mm Hg)	149 ± 28	154 ± 30	0.40
Heart rate (bpm)	85 ± 23	77 ± 18	0.04
Killip class > 1	8 (28%)	70 (17%)	0.13
LV ejection fraction < 45%	5/26 (19%)	59/383 (15%)	0.60
ST-segment depression	12 (41%)	146 (34%)	0.44
Positive troponin	26 (90%)	259 (61%)	0.002
Three-vessel disease or left main coronary artery disease	19/26 (73%)	145/325 (45%)	0.005
In-hospital Treatment			
Aspirin	28 (97%)	419 (99%)	0.39
Clopidogrel	26 (90%)	395 (93%)	0.51
Low-molecular weight heparin	28 (97%)	377 (89%)	0.19
Unfractionated heparin	0	15 (3.5%)	0.30
GP IIb/IIIa inhibitor	4 (14%)	23 (5.4%)	0.07
Coronary angiography	26 (90%)	325 (76%)	0.10
Coronary angioplasty	15 (52%)	155 (36%)	0.10

STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; LV = left ventricle; GP IIb/IIIa inhibitor: glycoprotein IIb/IIIa inhibitor.

Table 2 – Association of in-hospital death with bleeding variables

	Death	No death	p value
Sample size	28	427	
Age (years)	76 ± 11	67 ± 13	< 0.001
Heart rate (bpm)	87 ± 20	77 ± 18	0.007
Positive troponin	27 (96%)	258 (60%)	< 0.001
Three-vessel disease or left main coronary artery disease	15/21 (71%)	149/330 (45%)	0.02
In-hospital treatment			
GP IIb/IIIa inhibitor	2 (7.1%)	25 (5.9%)	0.78
Coronary angiography	21 (7.5%)	330 (7.7%)	0.78
Coronary angioplasty	8 (29%)	162 (38%)	0.32

GP IIb/IIIa inhibitor: glycoprotein IIb/IIIa inhibitor

Table 3 – Propensity model for major bleeding

Variable	β Coefficient	Odds Ratio (95% CI)	p value
Age (years)	0.05	1.05 (1.01 – 1.09)	0.01
Heart rate (bpm)	0.88	1.01 (0.99 – 1.03)	0.32
Positive troponin	1.09	2.9 (0.86 – 10)	0.09
Three-vessel disease or left main coronary artery disease	1.0	2.7 (1.09 – 6.7)	0.03

Only variables occurring before bleeding and simultaneously associated with bleeding and death were tested. Significant variables (age and three-vessel disease or left main coronary artery disease) comprised the final propensity model, which showed satisfactory discriminating capacity (C-statistics = 0.76; P < 0.001).

Table 4 – Logistic regression analysis of the in-hospital death endpoint, assessing the predictive value of bleeding after adjusting for the propensity model

Variable	β Coefficient	Odds Ratio (95% CI)	p value
Major bleeding	0.05	3.3 (1.2 – 9.5)	0.02
Propensity model	7.16	1.29 (6.8 – 242)	0.007

Table 5 – Mechanism of death of the patients experiencing major bleeding during hospitalization

	Diagnosis	Type	Site	Chronology of bleeding	Mechanism of death
Patient # 1	NSTEMI	5	CAT	Before shock	Massive bleeding → hemorrhagic shock
Patient # 2	NSTEMI	3a	CAT	After shock	Refractory angina → cardiogenic shock
Patient # 3	NSTEMI	3a	Gastrointestinal	After APE	APE → mechanical ventilation → sepsis
Patient # 4	STEMI	3a	Nasal	Before angina	Refractory angina → cardiogenic shock
Patient # 5	STEMI	3a	Angioplasty	Before renal dysfunction	Post-contrast acute renal failure
Patient # 6	STEMI	3b	Angioplasty	Before CABG	Complications of CABG

NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; CAT = cardiac catheterization; APE = acute pulmonary edema; CABG = coronary artery bypass grafting.

Discussion

The present study assessed the clinical impact of hemorrhagic events occurring during hospitalization due to ACS, and evidenced two major results: major bleeding during ACS associates independently with in-hospital mortality; and the individualized analysis of the sequence of events leading patients who bled to death indicates that the minority of deaths is directly or indirectly caused by the bleeding.

Regarding the first observation, the risk of death was four-fold greater in patients who bled during hospitalization as compared with those who did not. Considering the possibility that the factors leading to bleeding might be the same predisposing to death, the association observed could result from a confounding effect. Thus, a propensity score for bleeding was created and, after adjusting for it, bleeding remained as an independent predictor of in-hospital death. Although that independence has been described in several multicenter registries[6-11], this is the first Brazilian study to reproduce that information.

Although the independent association is one of the criteria required to define causality, it does not represent a sufficient condition. Thus, the independent prediction of death based on bleeding, already described in large multicenter registries, does not necessarily indicate that deaths result from hemorrhagic events. The causality of that association is only an inference suggested in previous studies, which could not be solved with only multivariate analysis. To solve that question in an unprecedented way, we performed a descriptive analysis of the sequence of events preceding death. That analysis provided the clear perception that bleeding acts predominantly as a risk marker, and only secondarily as a risk factor for death. Six deaths occurred after major bleeding: in two, the conditions of recurrent ischemia and heart failure that led to death had installed before the hemorrhagic event; in a third case of death due to heart failure, the nasal bleeding (with no hemodynamic repercussion) preceded the manifestation of ventricular dysfunction by days; in a fourth case, the death resulted from dialysis complications; in a fifth case, death resulted from post-operative complications of coronary artery bypass grafting. Thus, in only one case, death resulted definitively

from bleeding, which led the patient to hemorrhagic shock and consequent myocardial infarction. It is worth emphasizing that the previous studies have not used that type of analysis probably due to logistic difficulty in performing such a detailed assessment in large and multicenter studies, which use only dichotomous information regarding the prediction and endpoint variables.

Thus, it is evident that logistic regression or Cox analyses, using isolated covariables or propensity scores, are not sufficient to completely adjust the effect of bleeding for confounding factors. After those analyses, the effect of residual confusion probably maintains an overestimated association between bleeding and death. In reality, bleeding seems an excellent risk marker, because of its relationship with several characteristics of the patient, increasing the patient's vulnerability to fatal endpoints. In this context, the recent *BARC*[13] has proposed that those events be classified into types 1 to 5, according to their consequences. Our study represents the first report about the distribution of the type of bleeding according to that classification, type 5 meaning that death resulted directly from bleeding.

It is worth noting that our study is in accordance with the current emphasis put on the need for measures to reduce hemorrhagic endpoints, such as rationalization of the antithrombotic therapy according to the risk/benefit analysis[15-17], use of safer pharmacological strategies[18-20], and special attention to the manipulation of puncture sites and femoral introducer sheaths[21]. Although the present study reduces the clinical impact of bleedings, it does not completely exclude their causal relationship with fatal events, because of the one death resulting from bleeding in this small-sample study. In addition, non-fatal hemorrhagic events cause discomfort, prolongation of the hospitalization time, need for blood transfusion and suspension of required agents. Thus, independently of their fatal potential, bleedings should be prevented.

Considering that most deaths do not result from bleeding, our study suggests that, in dichotomous situations, the clinical decision should prioritize the prevention of recurring ischemic events rather than the prevention of hemorrhage. For example, despite the high risk of bleeding (high CRUSADE Bleeding Score[22]), a patient at high risk for ischemia (GRACE Score[2]) should undergo an invasive strategy. Thus, assessing the risk of bleeding should stimulate preventive measures against bleeding, but should inhibit neither invasive procedures nor the intensity of the antithrombotic therapy in high-risk patients.

In addition, our study indicates that greater attention should be paid to prevent hemorrhages related to puncture sites, because they accounted for 80% of the cases of major bleeding. Some authors have reported that the digestive tract is the most frequent bleeding site[23]. However, hemorrhages occurring during hospitalization due to coronary syndromes should be differentiated from those occurring after hospital discharge. The studies reporting digestive bleeding as the most frequent one are those including the outpatient clinic follow-up[24-26]. Our data show clearly that, during hospitalization, bleeding related to the femoral puncture site, resulting from both angioplasty and diagnostic coronary angiography, is the most frequent.

The present study has some limitations that should be discussed. Despite the moderate sample size, considering the patients who bled, only six died. That small number resulted from the fact that we analyzed a small subgroup (death) inside another small subgroup (bleeding), making that limitation inherent to that type of analysis. Thus, we should recognize the sequential analysis as only a generator of hypothesis, which should be explored in further studies, whose cohorts contain information allowing the detailed assessment of the sequence of facts. In addition, this is a qualitative analysis, dealing with the clinical perception of causality, and lack of clear causal relationship was reported in five of the six cases. Although less likely, we should recognize that bleeding might have contributed indirectly to death in some cases.

In conclusion, the present study confirms the independent association between hemorrhagic events and in-hospital death. That association is primarily mediated by the effect of bleeding as a risk marker rather than a risk factor. That second observation should be considered as hypothesis generator to be confirmed by studies with larger samples.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any post-graduation program.

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