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Bleeding in non-ST-segment elevation acute coronary syndrome

Sangramento em síndrome coronariana aguda sem supradesnivelamento de segmento ST

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ABSTRACT

The development of antiplatelet and antithrombotic therapies, in addition to interventionist strategy, has resulted in great improvements in the outcomes of patients with non-ST-segment elevation acute coronary syndrome. Parallel to therapeutic advances, bleeding, which can be induced during management, increases the risk of recurrent ischemia, myocardial infarction and death. The present literature review describes the benefits and bleeding risks of each medication or intervention strategy and suggests guidelines for managing these patients.

Keywords: Bleeding/etiology; Acute coronary syndrome/complications; Gastrointestinal bleeding; Intracranial hemorrhages; Thrombosis; Transfusion

INTRODUCTION

Antiplatelet and antithrombotic agents, in addition to their role in interventional cardiology, have revolutionized the treatment of patients with non-ST-segment elevation acute coronary syndrome (NSTE ACS). However, the initial reduction of ischemic events in these patients has been associated with an increased incidence of bleeding. Major bleeding events increase mortality in-hospital (19.2% *versus* 1.5%),[1] at 30 days (10% *versus* 2.5%)[2] and at one year (35.9% *versus* 7.4%).[1] Furthermore, severe bleeding increases the risk of acute myocardial infarction (AMI),[1] stroke[1] and the need for urgent myocardial revascularization.[3] Therefore, bleeding has become the new challenge in managing NSTE ACS and has inspired the publication of two consensus statements.[4,5] However, neither of them provides much guidance on the management of complications and the risk-benefit ratio of using various antiplatelet and antithrombotic agents.

The purpose of the present study is to describe the bleeding risks associated with each medication or intervention and to suggest strategies for the management of patients with bleeding due to NSTE ACS.

DEFINITION OF BLEEDING

The poor outcome of patients with NSTE ACS has been well established for cases of major bleeding. However, evidence suggests that minor bleeding events also result in poor outcomes.[6] Several bleeding scores have been used in different studies, among which the TIMI (Thrombolysis in Myocardial Infarction) and GUSTO (Global Utilization of Strategies To Open occluded

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arteries) scores are prominent. The TIMI score was the first to be developed and is widely used; however, it has low sensitivity, given that hemoglobin needs to be reduced by 5 g/dL for bleeding to be considered severe.[7] The GUSTO score has a higher sensitivity and better correlation with death and reinfarction at 30 days and at 6 months compared to TIMI.[8] The variety of scores (Table 1) has complicated comparisons between studies.

With the purpose of standardizing the definitions of bleeding, North American institutions have recently created the Bleeding Academic Research Consortium (BARC).[9] This score stratifies bleeding on a scale from 0 (no bleeding) to 5 (fatal bleeding) and, as a major advantage, provides the ability to assess patients subjected to myocardial revascularization surgery (MRS).[9] Because BARC's definitions of bleeding have been achieved by consensus, it still requires validation, and new studies on ACS are encouraged to use this score together with previous scores so that such validation may be achieved in the near future.[9] For now, comparisons between studies of bleeding outcomes demand caution.

BENEFITS AND RISKS OF NSTE ACS TREATMENT

Knowledge of the risk-benefit ratio of the various tools used in the treatment of ACS is essential for the individualization of therapy (Table 2).

Acetylsalicylic acid (ASA) was one of the first medications assessed for the treatment of NSTE ACS and was established as a proven method after demonstrating a 56% reduction in cardiovascular death.[10] The antiplatelet effect of ASA is irreversible and results from its inhibition of thromboxane A2. In the long run, smaller daily doses of 75 to 100 mg provide the same benefit as do larger doses of 200 mg and reduce the incidence of major bleeding by 1.8%, according to the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) criteria.[11] The gastrointestinal tract is the most common site of bleeding caused by ASA, and its chronic use increases absolute risk by 0.12% a year.[12] Acetylsalicylic acid increases the risk of intracranial bleeding 1.65-fold for an increase in absolute annual risk of 0.03%.[12] Given the great benefit on mortality provided by ASA in treatment and secondary prevention, the risk of bleeding hardly justifies its non-prescription. Therefore, ASA is contraindicated only in cases of known hypersensitivity, active peptic ulcers, blood dyscrasias or severe liver disease.[13]

Clopidogrel, a thienopyridine, is an alternative for patients that are allergic to ASA. This group of drugs antagonizes platelet activation mediated by adenosine diphosphate (ADP), which acts on the P2Y12 receptor.[13] The combination of ASA and clopidogrel, at a loading dose of 300 mg, followed by 75 mg for maintenance, reduced the rate of cardiovascular death, AMI or stroke by 20% compared to ASA alone.[14] It should be noted that this benefit was due to the reduction in AMI.[14]

Dual antiplatelet therapy increases the incidence of severe bleeding, according to the CURE score.[14] The use of ASA alone at a dose of 100 mg in the CURE trial resulted in a bleeding rate of 1.9%, which increased to 3.0% when combined with clopidogrel. Daily doses of ASA above 200 mg increased the incidence of bleeding to 3.7% when used alone and to 4.9% when combined with clopidogrel.[14] However, this increase was not due

Table 1 - Criteria of the main bleeding scores for defining major bleeding in non-ST-segment elevation acute coronary syndrome

Scores	Bleeding site	Decrease in hemoglobin	Packed red blood cell transfusion	Death from hemorrhage	Others
TIMI*	Intracranial	Hb >5 g/dL	-	-	-
GUSTO	Intracranial	-	Need for transfusion associated with hemodynamic instability	Fatal hemorrhage	Hemodynamic instability
ACUITY	Intracranial or intraocular	Hb ≥3 g/dL and known source of bleeding; Hb ≥4 g/dL and unknown source	Need for transfusion	-	Hematoma >5 cm in diameter or need for on-site intervention
CURE	Symptomatic intracranial or intraocular with visual deficit	Hb ≥5 g/dL	≥2 U	Fatal hemorrhage	Hemodynamic instability or need for on-site intervention
OASIS-5	Symptomatic intracranial, intraocular or retroperitoneal	Hb ≥3 g/dL associated with frank hemorrhage	≥2 U	Fatal hemorrhage	-
OASIS-7	Symptomatic intracranial	Hb ≥5 g/dL	≥2 U	Fatal hemorrhage	Bleeding related to myocardial revascularization surgery
PLATO*	Intracranial and cardiac tamponade	Hb ≥5 g/dL	≥4 U	Fatal hemorrhage	Hemodynamic instability

Adapted from: Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators et al.,[6] Steinhubl et al.,[7] Peters et al.,[11] CURRENT-OASIS 7 Investigators et al.,[17] Antman et al.,[18] Wallentin et al.,[20] Ferguson et al.,[25] Stone et al.[27] Hb - serum hemoglobin. * Scores that also include patients with non-ST-segment elevation acute coronary syndrome.

Table 2 - Treatment of non-ST-segment elevation acute coronary syndrome and risk of bleeding

Drug	Score used	Incidence of severe bleeding (absolute) (%)	Incidence of severe bleeding (relative)	Reason for increased/decreased bleeding
ASA ≥200 mg *versus* ≤100 mg	CURE	3.7 *versus* 1.9	-	Increased bleeding leading to risk of death and GIT bleeding
Clopidogrel 300/75 mg + ASA 100 mg *versus* ASA 100 mg alone	CURE	3.0 *versus* 1.9	1.38 (1.13-1.67)	Increased need for transfusion of 2 U of packed red blood cells
Clopidogrel 600 mg/150 mg/75 mg *versus* conventional dose *I	CURRENT-OASIS-7 TIMI	2.5 *versus* 2.0 1.7 *versus* 1.3	1.24 (1.05-1.46) 1.26 (1.03-1.54)	Increased need for transfusion of 2 U of packed red blood cells
Prasugrel 60 mg/10 mg *versus* clopidogrel at conventional dose*	TIMI Associated with MRS	2.4 *versus* 1.8 13.4 *versus* 3.2	1.32 (1.03-1.68) 4.73 (1.90-11.82)	Increased fatal bleeding Increased bleeding related to MRS
Ticagrelor *versus* clopidogrel at conventional dose *	PLATO TIMI	11.6 *versus* 11.2 7.9 *versus* 7.7	1.04 (0.95-1.13) 1.03 (0.93-1.15)	There was no increase in total severe bleeding, although there was increased bleeding unrelated to MRS
Abciximab *versus* placebo	TIMI	1.4 *versus* 1.4	1.00 (0.5-1.08)	There was no increase in major bleeding
Prolonged tirofiban *versus* tirofiban for short period	TIMI	3.9 *versus* 3.0	1.31(0.46-3.7)	There was no intracranial bleeding
Unfractionated heparin *versus* ASA alone	Hb reduction by 2 g/dL and need for transfusion	-	1.99 (0.52-7.65)	Increased need for transfusion and reduced Hb
Enoxaparin *versus* UFH	TIMI GUSTO	9.1 *versus* 7.6 2.7 *versus* 2.2	-	Increased bleeding related to MRS
Bivalirudin *versus* UFH or enoxaparin associated with GPIIb/IIIa inhibitors	ACUITY TIMI	11.8 *versus* 9.1 1.9 *versus* 0.9	0.53 (0.43-0.65)	Reduced retroperitoneal and puncture site bleeding, decrease in Hb and need for transfusion
Fondaparinux *versus* enoxaparin	OASIS-5 TIMI	2.2 *versus* 4.1	0.52 (0.44-0.61) 0.55 (0.41-0.74)	Reduced fatal bleeding, retroperitoneal bleeding, requiring surgical intervention or transfusion. Did not reduce intracranial bleeding
Early invasive strategy *versus* initially conservative	-	4.2 *versus* 2.8	1.65 (1.20-2.26)	Increased puncture site bleeding
Radial route *versus* femoral route *,**	-	0.05 *versus* 2.3	0.27 (0.16-0.45)	Reduced puncture site bleeding

Adapted from: Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators et al.,[6] Peters et al.,[11] CURRENT-OASIS 7 Investigators et al.,[17] Antman et al.,[18] Wallentin et al.,[20] Kastrati et al.,[22] Neumann et al.,[23] Ferguson et al.,[25] Stone et al.,[27] Koreny et al.[33] ASA - acetylsalicylic acid; GIT - gastrointestinal tract; MRS - myocardial revascularization surgery; Hb - hemoglobin; UFH - unfractionated heparin; GP inhibitors - glycoprotein inhibitors. * Studies that also evaluated patients with non-ST-segment elevation acute coronary syndrome; ** Study evaluating percutaneous coronary intervention in patients with stable disease.

to fatal bleeding or hemorrhagic stroke, but rather to the need for packed red blood cell transfusions, and the most common sites of bleeding were arterial puncture sites and the gastrointestinal tract.[14]

The discontinuation of clopidogrel 5 days before MRS did not increase the risk of surgical bleeding.[14] The risk of bleeding increased 1.53-fold when clopidogrel was discontinued less than 5 days before surgery.[14]

Clopidogrel is a pro-drug that requires liver metabolism for its activation, bringing with it the inconvenience of a non-responder rate of approximately 20%.[15] Increasing the loading dose to 600 mg, followed by 150 mg per day for 6 days, and maintenance with 75 mg per day, improved antiplatelet activity.[16] However, this effect did not result in event reduction,[17] and the higher dose increased severe bleeding by 0.5%. It should be noted that this increase was due to a greater need for blood transfusions and not to fatal or intracranial bleeding.[17]

Prasugrel, another thienopyridine, had a non-responder rate of 3% at the loading dose of 60 mg.[15] Prasugrel reduced fatal (0.4% *versus* 0.7%) and nonfatal AMI (7.4% *versus* 9.4%) in addition to preventing *stent* thrombosis (1.1% *versus* 2.4%) compared with clopidogrel at the conventional dose for treating ACS in patients subjected to an early invasive strategy.[18] However, the more potent antiplatelet aggregation was associated with a 1.32-fold increase in the incidence of major bleeding, with increased fatal bleeding (0.4 *versus* 0.1%).[18] Prasugrel increases the risk of bleeding related to MRS by 10%.[18] When evaluating net benefit, patients older than 75 years, weighing less than 60 kg or with a history of stroke or transient ischemic attack (TIA) did not benefit from the use of prasugrel.[18]

Thienopyridines irreversibly inhibit P2Y12 receptors; this inhibition is reversible when using ticagrelor, a cyclopentyl-triazolo-pyrimidine.[19,20] Because it does not require liver metabolism for its antiplatelet activity, drug resistance does not occur and its onset of action is faster.[19] In patients with ACS, regardless of being subjected to the early invasive strategy, ticagrelor as compared to clopidogrel reduced the incidence of vascular death, AMI or stroke by 16%. Ticagrelor resulted in a 21% reduction of vascular death and a 16% reduction in AMI.[20] Ticagrelor is, therefore, the first antiplatelet agent shown to reduce total death rate and cardiovascular death since studies with ASA.

Unlike prasugrel, ticagrelor did not increase the total incidence of major bleeding; however, it did result in a 1.19-fold increase in bleeding unrelated to MRS, according to the PLATO (Platelet Inhibition and Patient Outcomes) criteria, and a 1.25-fold increase according to the TIMI criteria.[20] It also resulted in increased fatal intracranial bleeding (0.1% *versus* 0.01%).[20] Considering the NNT (number needed to treat) of 53 and the NNH (number needed to harm) of 142 for major bleeding, the net benefit favors the substitution of clopidogrel for ticagrelor.[20]

The benefit of glycoprotein GPIIb/IIIa inhibitors has been restricted to high-risk NSTE ACS patients with low risk of bleeding.[21] The best time to initiate their use is in the catheterization lab, given that these drugs primarily benefit patients undergoing angioplasty.[21] The use of high doses of GPIIb/IIIa inhibitors and the lack of adjustment of unfractionated heparin (UFH) initially resulted in unacceptable bleeding rates. The correction of the UFH dose and reduction of GPIIb/IIIa inhibitors doses led to the improvement of safety profiles for these drugs.[21]

The addition of ASA and clopidogrel, with a loading dose of 600 mg, to abciximab administered in the hemodynamics room to patients with AMI; without ST elevation and subjected to percutaneous treatment, reduces the incidence of death or AMI by 25% compared to placebo.[22] Under these conditions, abciximab did not result in major bleeding increase, presenting with a 1.4% bleeding risk as defined by the TIMI score.[22]

The combined use of ASA, clopidogrel (at a loading dose of 600 mg) and tirofiban was assessed in the ISAR-COOL (Intracoronary Stenting With Antithrombotic Regimen Cooling-Off) trial.[23] The absolute incidence of major bleeding was 3.9% in the group subjected to early intervention and 3% in the control group, with no occurrence of intracranial bleeding.

The lower risk of bleeding and greater number of studies with abciximab makes this the GPIIb/IIIa inhibitor of choice in interventions. The combination of ASA, clopidogrel and tirofiban prior to percutaneous intervention is a reasonable choice for patients with refractory ischemia and low risk of bleeding, and tirofiban can be used in cases where clopidogrel is contraindicated.[21,23]

Anticoagulants in combination with antiplatelet medication play an important role in the treatment of NSTE ACS. The first anticoagulant studied was UFH, which binds to antithrombin with consequent neutralization of thrombin and factor Xa.[13] When compared to ASA alone, the combination of UFH and ASA reduced the risk of AMI and death by 33%.[24] However, a 1.99-fold increase in major bleeding events was attributable to reduced hemoglobin and an increased need for blood transfusions.[24]

Only one third of UFH molecules (those with a minimum of 18 polysaccharide units, corresponding to approximately 6,000 Daltons) have anticoagulant activity.[13] The polysaccharide chains of UFH can be depolymerized to obtain low molecular weight compounds. These compounds are generally called low-molecular-weight heparins (LMWH), among which enoxaparin is the most widely studied in NSTE ACS.[13] The SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein inhibitors) trial showed the non-inferiority in the efficacy endpoint of enoxaparin compared to UFH.[25] Major bleeding, as defined by the TIMI score, was increased by approximately 1.5% with the use of enoxaparin; however, it was not increased when assessed with the GUSTO criteria.[25] This difference between scores occurred because enoxaparin induced a reduction in hemoglobin in MRS but did not increase intracranial bleeding or cause hemodynamic instability.[25] The increased bleeding found in the studies was possibly due to crossover between UFH and enoxaparin.[25] Crossover between heparins is therefore discouraged during treatment for NSTE ACS.[21] Hence, combining non-inferiority and convenient posology, and considering that the increased bleeding does not determine risk of immediate death or neurological sequelae, enoxaparin has become the most widely used heparin for the treatment of NSTE ACS.

Because there is a risk of overestimation when calculating the dose of enoxaparin for obese individuals and patients with renal dysfunction, it is prudent to monitor anti-Xa activity. Values of anti-Xa activity >1.8 IU/mL increase severe bleeding and values <0.5 result in increased risk for thrombosis.[26] An alternative for these patients is UFH, which has a more widely spread monitorization.

Bivalirudin, a direct thrombin inhibitor, proved effective in reducing major bleeding by 1 and 3%, when assessed with TIMI and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) scores, respectively. The comparison was made between bivalirudin and UFH or bivalirudin and enoxaparin combined with a GPIIb/IIIa inhibitor, for the treatment of NSTE ACS.[27] The benefit of bivalirudin on safety occurs without compromising its effectiveness on thrombotic outcomes, but it does not result in a reduction of cardiovascular events.[27]

Finally, fondaparinux, the only selective inhibitor of activated factor X available for clinical use, reduced mortality at 30 days (2.9% *versus* 3.5%) and at 6 months (5.8% *versus* 6.5%) compared to enoxaparin.[6] The impact

on mortality is related to the reduction in major bleeding by 48% within the first 9 days of follow-up, which was maintained after 6 months of treatment. The OASIS-5 (Organization to Assess Strategies in Acute Ischemic Syndromes 5) trial showed that fondaparinux reduced all types of bleeding included in the study's definition, except for intracranial bleeding.[6] However, OASIS-5 was performed before the SYNERGY data had been published, when the harmfulness of the crossover between heparins was not yet known. The use of UFH had, therefore, been recommended during angioplasty procedures, if the interval since the last dose of the drug under assessment was above 6 hours. At the end of the study, the frequency with which the group treated with enoxaparin received UFH was 10% higher than that of the fondaparinux group.[6] The authors advocated that the increased bleeding observed in the group treated with enoxaparin cannot be explained by the crossover between heparins.[6] This was based on the fact that the benefit was maintained in a subgroup analysis of patients who did not receive UFH. It was concluded that, although the major guidelines for the management of NSTE ACS[21,28] present fondaparinux with a Class I indication, the concept that fondaparinux reduces bleeding in this population may be mistaken. This drug was not retested against enoxaparin without the use of UFH during angioplasty. Moreover, it should be noted that enoxaparin also has a Class I indication in the same consensus statement.[21,28] Finally, patients treated with fondaparinux must receive an additional bolus dose of 80 IU/kg of UFH during percutaneous intervention to reduce the risk of catheter thrombosis, which increases from 0.4% to 0.9% compared to enoxaparin.[6,29]

Although there is much discussion about which medications provide better risk-benefit ratios in the treatment of NSTE ACS, it should be noted that one of the most common causes of bleeding is the use of inadequate doses of anticoagulant and antiplatelet medications. A recent report showed that 42% of patients with ACS received at least one antithrombotic drug in excess, and up to 15% of substantial bleeding events are thought to result from incorrect doses of medications.[30] Another precaution in the use of the newer anticoagulants is that, after substantial bleeding occurs, these drugs lack specific antidotes, unlike the well-known protamine used to reverse the effects of UFH (Table 3).

An early invasive strategy in NSTE ACS reduces the absolute risk of cardiovascular death or nonfatal AMI by 19% (absolute risk reduction of 3.2%) over 5 years.[31] The benefit is even greater in the population with high-risk NSTE ACS.[3]

Early invasive management is also estimated to increase the risk of severe bleeding by 2.4%.[32] The most common site of bleeding is the actual puncture site, and complications range from hematoma and arteriovenous fistula to pseudoaneurysm and retroperitoneal bleeding.[33]

TREATMENT OF BLEEDING IN NSTE ACS

Upper gastrointestinal bleeding (UGIB) is the most common form of bleeding in ACS, and the most feared is intracranial bleeding.

There have been no studies on the treatment of patients with UGIB due to ACS. However, the guidelines suggested by Tan et al.[34] for patients with UGIB on prolonged antiplatelet therapy, after percutaneous intervention, appear suitable as a guide for evaluating patients with NSTE ACS. The authors suggest the use of proton pump inhibitors and the discontinuation of ASA and clopidogrel during the first 24 hours of bleeding because this period without antiplatelet agents does not appear to increase the risk of ischemic events. The goal is to determine the risk of recurrent bleeding and death, which is given by the Rockall score[35] by combining esophagogastroduodenoscopy (EGD) data with clinical parameters (Table 4).[34]

If the Rockall score is < 5, the risk of recurrent bleeding (15%) and death (5%) are low.[35] Therefore, the recommendation is to restart dual antiplatelet therapy.[34] Higher scores reflect in increased risk of recurrent bleeding and death,[35] suggesting the discontinuation of ASA for 2 weeks due to its antiplatelet effect and harmful effect on the gastrointestinal mucosa. In these cases, clopidogrel should be used alone.[34]

The risk of stent thrombosis must be carefully assessed in cases of continuous bleeding, and the presence of ventricular systolic dysfunction, diabetes mellitus, renal failure, a stent greater than 20 mm in length, coronary intervention less than 3 months prior for metal stents or less than 12 months prior for drug-eluting stents constitute high risk situations. The site of stent implantation and the myocardial area at risk should be considered. If the risk of bleeding is considered greater than the risk of stent thrombosis, the discontinuation of ASA and clopidogrel is recommended, although with daily reassessments, aiming at resuming clopidogrel within 1 to 2 weeks.[34]

It should be noted that the discontinuation of ASA confers a 1.8-fold increase in the risk of stent thrombosis. The discontinuation of clopidogrel and ASA in patients with drug-eluting stents within the first 30 days of follow-up confers a 29% risk of thrombosis.[34]

No studies have been conducted to assess the treatment

Table 3 - Recommendations for using antidotes to reverse anticoagulants and antiplatelet agents

Anticoagulant	Time to restore hemostasis after discontinuation	Antidote	Dose	Pharmacokinetics	Monitoring	Considerations
UFH	3-4 hours	Protamine sulfate	1 mg for every 100 U of UFH administered over the past 4 hours. The half-life of heparin should be considered	Maintain dose below 100 mg in 2 hours; initially administer 50% of the dose, with subsequent doses titrated according to bleeding response	aPTT	Administer slowly (up to 5 mg/ minute) to reduce the risk of hypotension and bradycardia
LMWH	12-24 hours	Protamine sulfate	1 mg for every 1 mg of enoxaparin administered over the past 4 hours; the half-life of LMWH should be considered	Maintain dose below 100 mg in 2 hours; initially administer 50% of the dose, with subsequent doses titrated according to bleeding response	aPTT, PT, anti-Xa activity	Administer slowly (up to 5 mg/ minute) to reduce the risk of hypotension and bradycardia
		Recombinant Factor VIIa	90 μg/kg, but with no consensus	Immediate effect, duration of 2 to 6 hours		Case report studies
Factor Xa inhibitors	Fondaparinux: 24-30 hours	Recombinant Factor VIIa	90 μg/kg, but with no consensus	Immediate effect, duration of 2 to 6 hours	aPTT, PT/INR, time for thrombin formation, endogenous prothrombin potential and thromboelastography	Assessed in healthy volunteers only, with no active bleeding
	Idraparinux: 5-15 days	aPCC	20 U/kg, but with no consensus	Effect in minutes, duration of 12 to 24 hours		
Direct thrombin inhibitors	In general, approximately 12 hours		0.3 μg/kg diluted in saline, administer in 15 minutes	Immediate effect, dose can be repeated at 8 to 12-hour intervals	NR, aPTT and thrombin time	Repeated doses are associated with tachyphylaxis, hyponatremia and seizures, especially in children below 2 years of age
			At least 10 U			10 U of cryoprecipitate increases fibrinogen by approximately 0.7 g/L
			0.1 to 0.15 g/kg ε-aminocaproic acid IV for 30 minutes, followed by infusion of 0.5 to 1 g/hour until bleeding stops; or 10 mg/kg tranexamic acid IV every 6 to 8 hours until bleeding stops			Limited evidence regarding its efficacy
			Start with 2 U			
ASA	5-10 days		DDAVP	Effect in 15-30 minutes		
			Cryoprecipitate	Effect in 15-30 minutes		
			Antifibrinolytic agents			
			Fresh frozen plasma			
Clopidogrel	5 days	Platelet transfusion	DDAVP	Effect in 15-30 minutes		Can use DDAVP associated with platelet transfusion
			Platelet transfusion	Effect in 15-30 minutes		

Adapted from: Levi et al.[39] UFH - unfractionated heparin; aPTT - activated partial thromboplastin time; LMWH - low-molecular-weight heparin; PT - prothrombin time; aPCC - activated prothrombin complex concentrate; INR - international normalized ratio; IV - intravenous; ASA - acetylsalicylic acid; DDAVP - desmopressin.

Table 4 - Rockall score for risk of recurrent bleeding and death in patients with gastrointestinal bleeding

Score	0	1	2	3
Age (years)	<60	60-79	>80	-
Circulatory shock	Absent	HR >100 bpm	SBP <100 mmHg	-
Comorbidities	None	None	Heart failure	Kidney or liver failure
			Ischemic CMP	Advanced malignancy
Findings of the EGD	With no lesion OR Mallory-Weiss with no recent bleeding	All other findings	UGIT malignancy	-
Stigmata of recent hemorrhage	None or dark spots	-	Adhered clot Vessel visualization	-

Source: adapted from Tan et al.[34] and Rockall et al.[35] HR - heart rate; bpm - beats per minute; SBP - systolic blood pressure; CMP - cardiomyopathy; EGD - esophagogastroduodenoscopy; UGIT - upper gastrointestinal tract. Score ≤5: risk for recurrent bleeding ≤14.1% and risk of death ≤5.3%; score >5: risk of recurrent bleeding ≥24.1% and risk of death ≥10.8%.

of intracranial bleeding in patients with ACS. Analyses of the reversal of antiplatelet and anticoagulant treatment in the general population can assist therapeutic decisions.

The few studies of platelet transfusion for intracranial bleeding in patients on antiplatelet medication showed no benefits of transfusion on mortality. However, these were retrospective studies that did not specify the interval between admission and platelet administration or the dose used.[36] The morbidity due to intracranial bleeding should be weighed against the myocardial area at risk for thrombosis. If one opts for transfusion, the dose of 10 U of platelets is suggested after 300 mg of clopidogrel or 12.5 U after a loading dose of 600 mg.[37]

Platelet function can also be improved with the use of desmopressin or recombinant activated factor VII (rFVIIa). Both strategies were compared to platelet transfusion in patients presenting bleeding on cranial computed tomography scans following traumatic brain injury, and it has been suggested that transfusion is a superior method.[38] It is worth noting that the ability to reverse the antiplatelet effect of clopidogrel by desmopressin has been demonstrated *in vitro*, but has not yet been studied *in vivo*.[39] Furthermore, it is important to note that rFVIIa is associated with an increased risk of thrombosis,[40] its optimal dose has not yet been defined[41] and there is no standardized laboratory test to monitor its activity. The administration of rFVIIa is therefore recommended in cases of uncontrollable bleeding only (Table 3).[42]

The antiaggregation property conferred by glycoprotein IIb/IIIa inhibitors has a short duration when using tirofiban, which has a half-life of 6 hours. In contrast, abciximab can be found in the plasma up to 7 days after its administration. Platelet transfusion may reverse the effects of abciximab while waiting for its elimination; however, the antiaggregation conferred by tirofiban cannot be reversed by platelet transfusion.[43]

Most anticoagulant studies have involved oral anticoagulant therapy, although some of the patients included received heparin. Aggressive reversal of the international normalized ratio (INR) reduces mortality from 37 to 10%.[44] Therefore, the myocardial area at risk should be very significant to overcome the benefit of reversing anticoagulation. Aggressive therapy is recommended for the reversal of oral anticoagulation with the transfusion of fresh plasma, cryoprecipitate or prothrombin complex concentrates (PCCs).[45] Some guidelines include PCCs as first-line therapy for the reversal of oral anticoagulation, given their high efficacy and lower volume of administration (Table 3).[45]

There have been no studies on the use of protamine in patients with NSTE ACS. Its efficacy in reversing the anticoagulant effect of UFH is well established,[46] and it has a smaller effect on the reversal of enoxaparin (Table 3).

In addition to improving platelet function, rFVIIa reverses oral anticoagulation in minutes. The reduction of hematomas and consequent lower mortality have indeed been demonstrated in patients with intracranial bleeding on oral anticoagulant therapy.[47]

Regardless of location, profuse bleeding can result in tissue hypoxia and consequent systemic and myocardial ischemia. The transfusion of packed red blood cells is intended to correct this imbalance. Paradoxically, in the presence of NSTE ACS, the transfusion of packed red blood cells is associated with a higher incidence of AMI (25.2% *versus* 10%) and death (8% *versus* 3%).[48]

The cause of the higher mortality rate observed among patients with NSTE ACS who receive packed red blood cell transfusion is unclear. Both ischemia and a systemic inflammatory response appear to be involved.[48] When indicated, the transfusion of leukocyte-depleted red blood cells stored for less than 2 weeks may show benefits over regular transfusion.[5]

The threshold hemoglobin level for red blood cell transfusion in NSTE ACS remains unclear, ranging from 8 g/L[49] to 10 g/dl.[50] Individualization remains the best approach for red blood cell transfusion, including an assessment of anemia and risk for further blood loss, as well as the need to provide some reserve before tissue hypoxia is established.

The use of risk scores can identify patients at increased risk of bleeding and help choose medications for treating

Table 5 - CRUSADE score for risk of recurrent bleeding

Predictive factor	Score
Baseline hematocrit (%)	
<31	9
31-33.9	7
34-36.9	3
37-39.9	2
≥40	0
Creatinine clearance (mL/min)*	
≤15	39
15-30	35
30-60	28
60-90	17
90-120	7
>120	0
Heart rate (bpm)	
≤70	0
71-80	1
81-90	3
91-100	6
101-110	8
111-120	10
≥121	11
Gender	
Male	0
Female	8
Signs of HF on presentation	
Absent	0
Present	7
Previous vascular disease**	
Absent	0
Present	6
Diabetes mellitus	
Absent	0
Present	6
Systolic blood pressure (mmHg)	
≤90	10
91-100	8
101-120	5
121-180	1
181-200	3
≥201	5
Very low risk (%)	≤ 20
Bleeding - 3.1	
Death - 0.2	
Low risk (%)	21-30
Bleeding - 5.5	
Death- 0.8	
Moderate (%)	31-40
Bleeding - 8.6	
Death- 1.6	
High (%)	41-50
Bleeding -11.9	
Death- 3.2	
Very high (%)	>50
Bleeding - 19.5	
Death- 6.0	

Adapted from: Subherwal et al.[51] HF - heart failure. * Creatinine clearance calculated using Cockcroft-Gault's formula; ** previous vascular disease defined by history of peripheral arterial disease or cerebrovascular accident.

NSTE ACS. Among the bleeding risk scores developed, the CRUSADE bleeding score is the most widespread and provides different scores for each variable associated with hemorrhage, as shown in table 5.[51] It should be noted that these scores should not limit the use of medication, but help to individualize the treatment of NSTE ACS.

CLOSING REMARKS

Bleeding is the new challenge in treating NSTE ACS. Its presence implies worse patient outcomes, its prevention reduces the incidence of myocardial infarction and mortality and its treatment raises difficulties in the reestablishment of a balance between thrombosis and bleeding.

RESUMO

O desenvolvimento das terapias antiplaquetárias e antitrombóticas, bem como de uma estratégia intervencionista, resultou em grande melhora da evolução dos pacientes com síndrome coronariana aguda sem supradesnivelamento de segmento ST. Paralelamente ao avanço terapêutico, o sangramento, que pode ser induzido durante o manejo, aumenta o risco de isquemia recorrente, infarto e morte. Nesta revisão, descrevem-se o benefício e o risco de sangramento que cada medicamento ou estratégia de intervenção apresenta e sugerem-se condutas para o manejo desses pacientes.

Descritores: Sangramento/etiologia; Síndrome coronariana aguda/complicações; Hemorragia gastrintestinal; Hemorragias intracranianas; Trombose; Transfusão

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