Revista da
SOCESP
Sociedade de Cardiologia do Estado de São Paulo

UNSTABLE ANGINA AND NON-ST ELEVATION MYOCARDIAL INFARCTION: TREATMENT AND PROGNOSIS

ANGINA INSTÁVEL E INFARTO AGUDO DO MIOCÁRDIO SEM SUPRADESNIVELAMENTO DE ST: TRATAMENTO E PROGNÓSTICO

Paulo Vinícius Ramos Souza[1,2]
Patrícia Oliveira Guimarães[1,2]
Gustavo André Boeing Boros[1,2]
Alexandre de Matos Soeiro[1,2]

[1]Emergency Clinical Unit - InCor - HCFMUSP, São Paulo, SP, Brazil
[2]BP Mirante Hospital, São Paulo, SP, Brazil

Correspondence:
Alexandre de Matos Soeiro
Dr. Eneas de Carvalho Aguiar, 44.
Cep 05403-900 - Cerqueira César, São Paulo, Brazil
alexandre.soeiro@bol.com.br

Received on 09/14/2018
Accepted on 11/20/2018

ABSTRACT

Cardiovascular diseases are the main cause of death in the adult population worldwide, with acute coronary syndrome (ACS) being the most prevalent. We know that, presently, from an epidemiological point of view, non-ST elevation ACS is the most frequent form of clinical presentation of ACS, in about 62% of cases. Recently, important advances regarding antiplatelet and anticoagulant therapy exist, capable of reducing mortality associated with coronary heart disease. Moreover, early invasive stratification has played a key role in the improvement in prognosis. Thus, the choice of therapy and stratification should be evaluated individually and can modify short- and long-term outcomes.

Keywords: Acute Coronary Syndrome; Treatment; Prognosis.

RESUMO

Objetivo: As doenças cardiovasculares são responsáveis pela principal causa de óbitos na população adulta mundial, sendo a síndrome coronariana aguda (SCA) a mais prevalente entre elas. Resultados: Sabemos que hoje, do ponto de vista epidemiológico, a coronariopatia aguda sem supradesnivelamento de ST tornou-se a forma mais frequente de apresentação clínica da SCA, aproximadamente, em 62% dos casos. Nos últimos anos, houve importantes avanços em relação à terapêutica antiplaquetária e anticoagulante capazes de reduzir a mortalidade associada à doença coronariana. Além disso, a estratificação invasiva precoce teve papel fundamental nesse incremento de prognóstico. Conclusão: Dessa forma, atualmente, a escolha terapêutica e de estratificação devem ser avaliadas individualmente e podem modificar desfechos em curto e longo prazo.

Descritores: Síndrome Coronariana Aguda; Tratamento; Prognóstico.

INTRODUCTION

Cardiovascular diseases are the main cause of death of the world's adult population, with acute coronary syndrome (ACS) being the most prevalent disease.[1] In the United States, a person dies of coronary disease every 1 minute.[2]

We divided ACS into ST-elevation acute myocardial infarction (STEAMI) and non-ST elevation acute myocardial infarction (non-STEAMI), with the latter consisting of STEAMI and unstable angina (UA).

We know that today, from an epidemiological point of view, non-STEAMI is the most frequent form of clinical presentation of ACS,[1] accounting for about 62% of cases as indicated by the GRACE multinational registry.[3]

The difference between STEAMI and non-STEAMI is purely electrocardiographic, marked by the presence or absence of ST elevation. The differential diagnosis between STEAMI and UA, on the other hand, depends on the observation of peak levels of markers of myocardial necrosis.

PHARMACOLOGICAL TREATMENT OF NON-STEAMI

Platelet Antiaggregation

Antiplatelet therapy is among the main therapeutic approaches in ACS. The three main classes of antiaggregants act on different mechanisms in the activation of platelet aggregation.[4] Over the years, major studies have shown significant reductions in mortality and reinfarction rates,[5] thus, these drugs should be introduced as early as possible.

Acetylsalicylic acid (ASA) was shown to be effective in patients with UA and STEMI. The incidence of AMI or death was considerably reduced in four large randomized trials

 http://dx.doi.org/10.29381/0103-8559/20182804403-8

conducted before angioplasty became popular.[6-9] The CURRENT-OASIS 7[10] study found no statistically significant differences when high (300–325 mg/day) or low (75–100 mg/day) doses of ASA were used among patients who were invasively stratified. For all patients with ACS, an attack dose of 150–300 mg followed by 100 mg/day is recommended since they no longer use ASA.

Double antiplatelet therapy (ASA and clopidogrel; DAPT) has been shown to reduce ischemic coronary events in patients with STEMI compared to antiplatelet monotherapy (ASA only).[11,12] Current scientific evidence shows that more than 10% of patients treated with DAPT experience recurrent ischemic events in the first year after ACS and about 2% have stent thrombosis.[13] This is due to incomplete platelet inhibition and an inadequate response of some individuals to clopidogrel. We know that due to genetic polymorphism,[14] some patients are hypo- or hyper-responders to clopidogrel,[15] which may directly influence the drug's efficacy.

Clopidogrel should be used in the initial care of all cases of ACS except for rare exceptions in which the immediate need for revascularization surgery is considered. An attack dose of 300–600 mg followed by a dose of 75 mg/day is recommended[16] (patients with high ischemic risk and low risk of bleeding who underwent percutaneous treatment can receive 150 mg/day for 7 days with a subsequent dose reduction[10]).

The PLATO study[17] randomized 18,624 high-risk non-STEMI or STEMI patients, giving them an attack dose of 300-600 mg clopidogrel followed by 75 mg/day or an attack dose of 180 mg ticagrelor followed by 90 mg twice daily. It is worth remembering that patients who underwent percutaneous coronary intervention (PCI) were randomized to receive an additional dose of 300 mg of clopidogrel (completing 600 mg) or placebo.

In the non-STEMI subgroup (n = 11,080), the primary outcome, composed of cardiovascular death, AMI, or stroke, was significantly reduced with ticagrelor 10.0% vs. 12.3% (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.74–0.93; $P = 0.0013$) with similar reductions for cardiovascular death (3.7% vs. 4.9%; HR, 0.77; 95% CI, 0.64–0.93; $P = 0.0070$) and all-cause mortality (4.3% vs. 5.8%; HR, 0.76; 95% CI, 0.64–0.90; $P = 0.0020$). Therefore, compared to clopidogrel, ticagrelor could reduce mortality and is currently considered a first-line drug. It should be discontinued for 5 days before elective surgeries.

The TRITON study[18] tested prasugrel with an attack dose of 60 mg followed by 10 mg/day against and an attack dose of 300 mg of clopidogrel followed by 75 mg/day in patients with ACS (non-STEMI or STEMI) who underwent PCI. Among the 10,074 non-STEMI patients, there was a reduction in the recurrence of cardiovascular events in the prasugrel arm after 15 months of follow-up (from 11.2% to 9.3%; relative risk [RR], 0.82; 95% CI, 0.73–0.93; $P = 0.002$), followed by a significant reduction in AMI (from 9.2% to 7.1%; RR, 23.9%; 95% CI, 12.7–33.7; $P < 0.001$).

Due to the marked reduction that prasugrel showed in stent thrombosis in the TRITON study (1.13% prasugrel arm vs. 2.35% in the clopidogrel arm; HR, 0.48; 95% CI, 0.36–0.64; $P < 0.0001$) and in patients with pharmacological stents (0.84% vs. 2.31%, respectively; HR, 0.36; 95% CI, 0.22–0.58; $P < 0.0001$), prasugrel should be considered in addition to clopidogrel therapy for patients with stent thrombosis.

It should only be prescribed after knowledge of the coronary anatomy. Thus, its routine use in initial patient care is not indicated. Such evidence comes from the ACCOAST study,[19] which showed no reduction in the rate of major ischemic events in up to 30 days, an increased bleeding rate in non-STEMI patients, and catheterization scheduled in those who received pre-treatment with prasugrel.

Prasugrel should not be used in elderly (>75 years) or low-weight (<60 kg) patients and is contraindicated in those with a previous history of stroke or transient ischemic attack. If the treatment is surgical, it should be suspended for at least 7 days before coronary artery bypass grafting surgery.

A meta-analysis of six large trials[20] of 29,570 non-STEMI patients showed a relative risk reduction (RRR) of 9% in death or non-fatal AMI with the use of GP IIbIIIa inhibitors (10.7% vs. 11.5%; $P = 0.02$) when combined with heparin. The great benefit of this drug was observed in patients who underwent PCI (10.5% vs. 13.6%; OR, 0.74; 95% CI, 0.57–0.96; $P = 0.02$). However, greater bleeding was observed, although not intracranial bleeding.

However, these studies made previous use of P2Y12 inhibitors; therefore, their use in clinical practice is at the discretion of the hemodynamicist physician and/or clinician responsible for the patient, especially in the presence of high thrombotic load, severe atheromatosis, reflow, or other thrombotic complications during the hemodynamic study, and provided that the patient has low hemorrhagic risk. In the eventual use of this drug when the patient needs surgical treatment, it must be discontinued and its effect is reverted after 6–8 hours.[21]

ANTICOAGULANTS

The literature consistently shows that anticoagulation in non-STEMI patients in combination with DAPT is more effective than either alone.[22] Several classes of anticoagulants have been approved or are under study for application in cases of ACS, each acting at different levels of the coagulation cascade.[16]

UNFRACTIONATED HEPARIN

An initial intravenous administration of 60 IU/kg (maximum 4000 IU) followed by the infusion of 12 IU/kg/h (maximum 1000 IU/h) is recommended. The level of anticoagulation is monitored by activated partial thromboplastin time every 6 hours and is considered therapeutic in the range of 50–70s, which corresponds to 1.5–2.5 times the upper limit of normal.[21]

It is an important therapeutic option in patients > 100 kg and in those with severe renal dysfunction (creatinine clearance rate < 15 mL/min/1.73 m^2). After PCI, medication should be routinely discontinued.[21]

LOW MOLECULAR WEIGHT HEPARIN

Enoxaparin is the most commonly used low molecular weight heparin in clinical practice. The recommended dose is 1 mg/kg administered subcutaneously every 12 hours (every 24 hours if the patient has a creatinine clearance rate < 30 mL/min/1.73 m^2). It should not be administered to

patients with a clearance < 15 mL/min/1.73 m^2; in elderly patients (>75 years), the dose administered should be 0.75 mg/kg every 12 hours. Anticoagulation monitoring with anti-Xa activity dosage is recommended in patients with more than 100 kg and creatinine clearance rate of 15–30 mL/min/1.73 m^2. [16]

In non-STEMI patients who were pre-treated with enoxaparin, no additional dose is recommended during PCI if the last subcutaneous dose administered was performed less than 8 hours before PCI. However, a bolus of intravenous enoxaparin 0.3 mg/kg is recommended if the last subcutaneous dose was administered more than 8 hours before the PCI.[23]

The meta-analysis that evaluated enoxaparin versus unfractionated heparin (UFH) in the context of non-STEMI patients undergoing PCI[24] showed a safety and efficacy profile of enoxaparin versus UFH with a significant reduction in death (RR 0.66; 95% CI, 0.57–0.76; $P < 0.001$), death or AMI (RR, 0.68; 95% CI, 0.57–0.81; $P < 0.001$), complications of AMI (RR, 0.75; 95% CI, 0.6–0.85; $P < 0.001$), and major bleeding (RR, 0.80; 95% CI, 0.68–0.95), $P = 0.009$).

The SYNERGY study[25] showed that more important than knowing the type of heparin to be used for the treatment of ACS without elevation is not changing the type of heparin chosen (UFH or low molecular weight heparin) in the same hospitalization, increasing the risk of associated bleeding.

For non-STEMI patients, the recommended dose is 2.5 mg subcutaneously once daily. It is contraindicated in patients with a creatinine clearance rate < 20 mL/min/1.73 m^2 and does not require monitoring with any exam or a supplementary dose.[16]

In the OASIS-5 study,[26] which included 20,078 non-STEMI patients, the use of fondaparinux 2.5 mg once daily showed rates not less than enoxaparin for death, AMI, or refractory ischemia in 9 days (HR, 1.01; 95% CI, 0.90–1.13; $P = 0.007$) and a significantly decreased rate of major bleeding (HR, 0.52; 95% CI, 0.44–0.61; $P < 0.001$). In the subgroup that underwent PCI ($n = 6,239$), a significant decrease in the rate of major bleeding (including puncture site complications) was observed at 9 days in the fondaparinux group (2.3% *vs.* 5.1%; HR, 0.45; 95% CI, 0.34–0.59; $P < 0.001$).

Catheter thrombosis was observed more frequently in patients who received fondaparinux (0.9%) than in those who received enoxaparin (0.4%), but this complication was avoided with the infusion of UFH at the time of PCI. [27]

RISK STRATIFICATION OF MAJOR CARDIAC EVENTS

In clinical practice, the most commonly used methods are the "punctual" stratification[21] (Table 1), TIMI[28] risk score (Figure 1), and GRACE risk score (Figure 2).[29,30] Stratifying the cardiac risk of all non-STEMI patients is important because of its direct association with the conduct to be taken. High-risk patients require early invasive stratification, while low-risk patients may undergo non-invasive stratification, even in an outpatient setting.

ULTRASENSITIVE BIOMARKERS

The introduction of ultra-sensitive cardiac troponin measurements instead of standard troponin tests increased the detection of myocardial infarction (~4% absolute and 20% relative increase) and a reciprocal decrease in the diagnosis of UA.[31] Compared to patients with STEMI, individuals with UA do not have myocardial necrosis; thus, they have a substantially lower risk of death and seem to obtain fewer benefits from intensified antiplatelet therapy as well as early invasive strategy.[32]

Table 1. Occasional stratification of the risk of death or AMI (acute myocardial infarction).

	High	Moderate	Low
Predictive variable	At least one of the following characteristics must be present	No high-risk characteristics, but with any of the following	No intermediate or high-risk characteristics, but with any of the following
History	Aggravation of symptoms in the last 48 hours. Patient aged ≥ 75 years	Patient aged 70-75 years	
		Previous infarction, cerebrovascular or peripheral disease, diabetes mellitus, vascularization surgery, previous use of ASA	
Precordial pain	Prolonged pain (≥20 min) at rest	Angina at rest ≥ 20 min resolved with probability of moderate to high CAD	New episode of CCS (canadian cardiovascular society) angina class III or IV in the previous 2 weeks without prolonged pain at rest but with moderate or high probability of CAD
		Angina at rest ≤ 20 min with spontaneous relief or using nitrate	
Physical examination	Pulmonary edema, worsening of or appearance of mitral regurgitation murmur, B3, new gasps, hypotension, bradycardia, or tachycardia		
Electrocardiography	ST depression ≥ 0.5 mm (whether associated with angina or not), dynamic alteration of the ST, complete blockade of new or presumed new branch	T wave inversion ≥ 2 mm; pathological Q waves	Normal or unchanged during the pain episode
	Sustained ventricular tachycardia		
Serum markers of ischemia	Markedly elevated (e.g., TnTC ≥ 0.1 ng/mL)	Slightly elevated (e.g., TnTc 0.03-0.1 ng/mL)	Normal

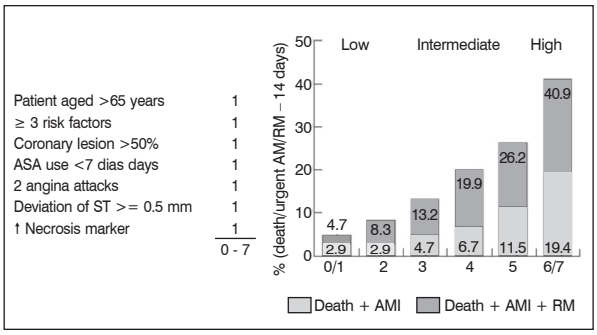

Figure 1. TIMI risk scores: low risk, 0-2 points; medium risk, 3-4 points; high risk, >5 points.

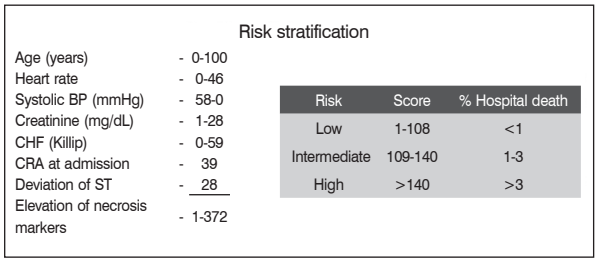

Figure 2. GRACE risk score.

TIME FOR INVASIVE STRATIFICATION ACCORDING TO RISK CRITERIA

In 2015, the European guideline for non-STEMI[6] introduced a new stratification category, named very high-risk patients, for patients who should receive invasive stratification very early (i.e. within less than 2 hours of diagnosis). High-risk patients would be invasively stratified within 24 hours, named early invasive stratification, while intermediate-risk patients should receive invasive stratification within 72 hours (Table 2).

In low-risk patients, if the serum markers are normal promptly and the patient does not experience pain recurrence, hospital discharge should be considered with referral for outpatient follow-up within 72 hours. However, ideally or in cases in which doubts persist regarding the clinical/electrocardiographic picture or association with several coronary risk factors, stratification using noninvasive tests (ergometry, myocardial scintigraphy, stress echocardiography, or coronary angiotomography) should be considered. In cases of negative tests, the patient must be followed up in the outpatient clinic. If ischemia or severe coronary obstruction is observed, the patient should be admitted for invasive stratification. [21]

STRATIFICATION OF BLEEDING RISK

Greater bleeding increases mortality rates in non-STEMI patients[33]; thus, every patient with non-STEMI should be stratified for bleeding risk. These data should be considered when choosing the best therapy and stratification. Several scores can be used, the most common being the Crusade[34] and Roxana scores.[35]

NON-STEMI in Special Populations

Elderly

In elderly patients, it is recommended that doses of antithrombotic drugs be stratified according to body weight and kidney function. Invasive strategies should be considered if appropriate, as is revascularization after the careful assessment of potential risks and benefits, life expectancy estimation, comorbidities, quality of life, fragility, values, and patient preferences.[36,37]

Table 2. Risk criteria that determine the invasive strategy in non-STEMI.

Very high-risk criteria - Invasive stratification within 2 h
- Cardiogenic shock or hemodynamic instability
- Angina recurrent or refractory to drug treatment
- Life-threatening arrhythmia or cardiorespiratory arrest
- Mechanical complications of AMI
- Acute heart failure
- Recurrent dynamic ST-T changes, particularly intermittent ST elevation
High-risk criteria - Invasive stratification within 24 h
- Increased or decreased cardiac troponin compatible with AMI
- Dynamic change of ST or T symptomatic or not
- GRACE score > 140
Intermediate risk criteria - Invasive stratification up to 72 h
- Diabetes mellitus
- Renal insufficiency (clearance < 60 mL/min/1.73 m^2)
- Left ventricular ejection fraction <40% or congestive heart failure
- Angina post-heart attack of recent onset
- Previous PCI
- Previous coronary artery bypass grafting surgery
- GRACE score between 140 and 109
- Low-risk criteria to assess the real need for invasive stratification
- Any characteristics not mentioned above

Diabetes mellitus

The glucose levels of every patient with non-STEMI, especially those already known to be diabetics, should be monitored. Levels > 180 mg/dL indicate that treatment is necessary, and hypoglycemia should be avoided. Invasive strategies should be preferred in these patients. If percutaneous treatment is chosen, pharmacological stents should be preferred to conventional stents.[38-41]

Chronic kidney disease

The doses of antithrombotic drugs should be adjusted for renal function as previously mentioned. Patients who will undergo an invasive strategy should be hydrated with isotonic saline and low osmolarity contrasts; the lowest possible infused volume should be preferred. As in the case of diabetic patients, once PCI is recommended, drug-eluting stents should be preferred for this population.[42,43]

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: Each author contributed individually and significantly to the development of the study. PVRS and AMS were the main contributors to the writing, while GABB and POG conducted the literature search and review.

REFERENCES

1. Braunwald E. Unstable angina and non-ST elevation myocardial infarction. Am J Respir Crit Care Med. 2012;185(9):924-32.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC Guideline for the management of patients with non–ST-elevation acute coronary syndromes. J Am Coll Cardiol. 2014;64(24):e139-228.
3. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA. The Global Registry of Acute Coronary Events, 1999 to 2009-GRACE. Heart. 2010;96(14):1095-101.
4. Aronow WS. Use of antiplatelet drugs in the treatment of acute coronary syndromes. Cardiovasc Hematol Disord Drug Targets. 2013;13(2):151-7.
5. Fuster V, Kalil Filho, R, Albuquerque, CP. Medicina cardiovascular, reduzindo o impacto das doenças. São Paulo: Editora Atheneu, 2016. 594 p.
6. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC group. Lancet. 1990; 336(8719): 827–30.
7. Lewis HD Jr , Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE 3rd, et al.. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration cooperative study. N Engl J Med. 1983;309(7):396–403.
8. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Lévy G, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med. 1988;319(17):1105–11.
9. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med. 1985;313(22):1369–75.
10. Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010;363(10):930–42.
11. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494–502.
12. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527–33.
13. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, et al. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA. 2011;306(11):1215–23.
14. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009; 360(4):363–75.
15. Matetzky S, Shenkman B, Guetta V, Shechter M, Beinart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004;109(25):3171–75.
16. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315.
17. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045–57.
18. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–15.
19. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med. 2013;369(11): 999–1010.
20. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes. Gradient of benefit related to the revascularization strategy. Eur Heart J. 2002; 23(18):1441–8.
21. Gianetti NS, Baracioli LM. Síndrome coronária aguda sem supradesnível do segmento ST. In: Soeiro, AM, Leal TCAT, Oliveira Jr MT, Kalil Filho R. (Org.). Manual de Condutas Práticas da Unidade de Emergência do INCOR. Barueri, SP: Editora Manoele Ltda. 2015,p. 38-53.
22. Eikelboom JW, Anand SS, Malmberg K, Weitz JL, Geinsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet. 2000;355(9219):1936–42.
23. Collet JP, Montalescot G, Lison L, Choussat R, Ankri A, Drobinski G, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation. 2001;103(5):658–63.
24. Silvain J, Beygui F, Barthélémy O, Pollack C Jr, Cohen M, Zeymer U, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2012;344:e553.
25. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA. 2004;292(1):45–54.
26. Jolly SS, Faxon DP, Fox KA, Afzal R, Boden WE, Widimsky P, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors or thienopyridines: results from the OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial. J Am Coll Cardiol. 2009;54(5):468–76.
27. Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, Rupprecht HJ, et al. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial. JAMA. 2010;304(12):1339–49.
28. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835–42.
29. Aragam KG, Tamhane UU, Kline-Rogers E, Li J, Fox KA, Goodman SG, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. PLoS One. 2009;4(11):e7947.
30. de Araújo Goncalves P, Ferreira J, Aguiar , Seabra-Gomes R . TIMI, PURSUIT, and GRACE risk scores: sustained prognostic

value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005;26(9):865–72.

31. Mueller C . Biomarkers and acute coronary syndromes: an update. Eur Heart J. 2014;35(9):552–6.
32. Bugiardini R, Manfrini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. Arch Intern Med. 2006;166(13):1391–95.
33. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dandas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55(23):2556–66.
34. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score. Circulation. 2009;119(14):1873–82.
35. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55(23):2556-66.
36. Bauer T, KoethO, Junger C, Heer T, Wienbergen H, Gitt A, et al. Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. Eur Heart J. 2007;28(23):2873–78.
37. Devlin G, Gore JM, Elliott J, Wijesinghe N, Eagle KA, Avezum A, et al.. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. Eur Heart J. 2008;29(10):1275–82.
38. O'Donoghue ML, Vaidya A, Afsal R, Alfredsson J, Boden WE, Braunwald E, et al. An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. J Am Coll Cardiol. 2012;60(2):106–11.
39. Roffi M, Topol EJ . Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2004;25(3):190–98.
40. Daemen J, Garcia-Garcia HM, Kukreja N, Imani F, de Jaegere PP, Sianos G, et al. The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus. Eur Heart J. 2007;28(1):26–32.
41. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schömig A, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ. 2008;337:a1331.
42. Tsai TT, Messenger JC, Brennan JM, Patel UD, Dai D, Piana RN. Safety and efficacy of drug-eluting stents in older patients with chronic kidney disease: a report from the linked CathPCI Registry-CMS claims database. J Am Coll Cardiol. 2011;58(18):1859–69.
43. Shenoy C, Boura J, Orshaw P, Harjai KJ. Drug-eluting stents in patients with chronic kidney disease: a prospective registry study. PLoSOne. 2010;5(11):e15070.