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REVIEW ARTICLE

Acute Coronary Syndromes: Treatment and Risk Stratification*

Síndromes Coronarianas Agudas: Tratamento e Estratificação de Risco

Antonio Eduardo Pereira Pesaro[1], Paulo Cesar Gobert Damasceno Campos[1], Marcelo Katz[1], Thiago Domingos Corrêa[2], Elias Knobel[3]

SUMMARY

BACKGROUND AND OBJECTIVES: Acute coronary syndromes result from a disruption of a vulnerable coronary plaque complicated by intraluminal thrombus formation, embolisation, and variable degrees of coronary obstruction. Patients with total occlusion may present with acute ST Elevation Myocardial Infarction (STEMI). Partial vessel obstruction may result in Non-ST-Elevation Acute Myocardial Infarction (NSTEMI) or unstable angina (UA). Clinical symptoms and electrocardiographic changes are the main components of identification of ACS. The rapid and effective triage of such patients regarding presence or absence of ST-segment elevation is critical to dictate further therapeutic strategies. The objective of this chapter was to review current evidence and recommendations for the evaluation and early treatment of acute coronary syndromes.

CONTENTS: We performed a clinical review using the electronic databases MedLine and LILACS from January 1990 to September 2007.

CONCLUSIONS: Reperfusion of the infarct-related artery is the cornerstone of therapy for STEMI. Fibrinolysis and percutaneous coronary intervention are both well established as effective options. Management of UA/NSTEMI patients requires early risk stratification. High-risk patients should undergo an early invasive strategy that consists in performance of cardiac catheterization in the first 24 to 48 hours of presentation.

Key Words: acute coronary syndromes, Non-ST elevation acute coronary syndrome, myocardial infarction, percutaneous coronary intervention, reperfusion treatment, risk stratification, ST elevation acute coronary syndrome, unstable angina

RESUMO

JUSTIFICATIVA E OBJETIVOS: As síndromes coronarianas agudas são resultado da ruptura de uma placa coronariana instável, complicada pela formação de trombo intraluminal, embolização e graus variáveis de obstrução coronária. Pacientes com oclusão total de uma artéria coronária apresentam infarto agudo do miocárdio (IAM) com supradesnivelamento do segmento ST. Uma oclusão parcial do vaso pode resultar em IAM sem supradesnivelamento do segmento ST ou angina instável. As manifestações clínicas e as alterações eletrocardiográficas são componentes fundamentais para identificação dos pacientes portadores destas síndromes. A triagem rápida e eficaz desses pacientes; quanto à presença ou não do supradesnivelamento do segmento ST, é fundamental para a determinação da estratégia terapêutica a ser empregada. O objetivo deste estudo foi realizar uma revisão da literatura sobre as evidências atuais e as recomendações

1. Assistant Physician - Intensive Care Unit Hospital Israelita Albert Einstein
2. Medical Resident - Intensive Care Unit Hospital Israelita Albert Einstein.
3. Vice-President of Medical affairs of the Board of Directors and Director Emeritus and Founder of the Intensive Care Unit Hospital Israelita Albert Einstein.

*Received from Intensive Care Unit of Hospital Israelita Albert Einstein, São Paulo (SP), Brazil.

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Address for correspondence:
Antonio Eduardo Pereira Pesaro, M.D.
Unidade Coronariana - Hospital Israelita Albert Einstein
Av. Albert Einstein, 627, Morumbi
05651-901 São Paulo, SP
Fone: (11) 3747-15003 / Fax: (11) 3742-2834
E-mail: antonioepp@einstein.br

para avaliação e tratamento das síndromes coronarianas agudas.
CONTEÚDO: Revisão da literatura, utilizando as bases eletrônicas de dados MedLine e LILACS, no período de janeiro de 1990 a setembro de 2007.
CONCLUSÕES: A reperfusão da artéria responsável pelo infarto é a etapa fundamental no tratamento de pacientes com infarto agudo do miocárdio com supradesnivelamento do segmento ST. A terapia trombolítica ou a intervenção coronariana percutânea são duas opções terapêuticas bem estabelecidas na literatura. Pacientes portadores de IAM sem supradesnivelamento do segmento ST ou angina instável necessitam de estratificação de risco precoce. Pacientes de alto risco devem ser submetidos à estratégia invasiva precoce, que consiste na realização do cateterismo cardíaco nas primeiras 24-48 horas do início dos sintomas.
Unitermos: angina instável, estratificação de risco, intervenção coronariana percutânea, reperfusão, síndromes coronarianas agudas, síndromes coronarianas agudas com supradesnivelamento do segmento ST, síndromes coronarianas agudas sem supradesnivelamento do segmento ST

INTRODUCTION

Acute coronary syndromes (ACS) result from a disruption of a vulnerable coronary plaque complicated by intraluminal thrombus formation, embolisation, and variable degrees of coronary obstruction[1].
ACS included a spectrum of clinical presentations. Patients with total occlusion may present with acute ST-Elevation Myocardial Infarction (STEMI) requiring emergency reperfusion therapy. Partial vessel obstruction may result in Non-ST Elevation Acute Myocardial Infarction (NSTEMI) or unstable angina (UA), that will require initial medical stabilization followed by judicious risk stratification for determination of therapeutic strategies (invasive or conservative)[1].
Ischemic heart disease accounts for nearly 1 million deaths in the United States annually. In industrialized countries, annual incidence of unstable angina is approximately 6 cases per 10,000 people. The overall mortality rates are approximately 30% for acute myocardial infarction (AMI). Half of the deaths occur in the first two hours of the event and 14% of the patients die before receiving medical care[2,3].
The purpose of this chapter is to review current evidence and recommendations for the evaluation and early treatment of acute coronary syndromes.

DEFINITION AND CLASSIFICATION OF ACUTE CORONARY SYNDROME

Patients without evidence of MI, but with typical ischemic syndrome are classified into the spectrum of UA with the possible following clinical presentations: rest angina, new-onset angina or increased angina pattern[4].
The definition of STEMI is a new, or presumed new, ST segment elevation in 2 or more contiguous leads of at least 2 mm at the J point in leads V1-V3, or 1 mm in other leads[5].
NSTEMI presentations represent a real diagnostic challenge. In those cases ECG changes may appear as ST segment depression, transient ST elevation or T wave inversion. Differentiation of NSTEMI from UA is based on marker of myocyte necrosis elevation in the former and absence of it in the latter[1,4].

SPECIFIC TREATMENT FOR ST-ELEVATION MYOCARDIAL INFARCTION

Perfusion

Reperfusion of the infarct-related artery is the cornerstone of therapy for STEMI. Fibrinolysis and percutaneous coronary intervention (PCI) are both well established as effective options, but PCI has generally come to be regarded as the treatment of choice[6]. It should be performed as soon as possible to minimize myocardial damage. The efficacy in the restoration and maintenance of optimal flow (TIMI 3) are directly related to the prognosis of myocardial infarction[7].
A recent meta-analysis of 23 randomized, controlled trials comparing PCI to fibrinolysis revealed that PCI reduced short-term mortality, non-fatal re-infarction, and stroke when compared to fibrinolysis[8].
The choice of reperfusion therapy depends on several factors: time delay to primary PCI (door-balloon time), pre-hospital delay, time to hospital fibrinolysis (door-needle time), contraindications and risks of fibrinolytic therapy, location and size of MI, presence of heart failure or cardiogenic shock (high-risk MI). However, the major factor to determine the choice of reperfusion is TIME, including time since symptom onset, time delay for transportation and time delay for primary PCI[9].
According to the ACC/AHA 2004 guidelines, it is not

possible to say that one modality is superior for all patients in all settings. There is also concern that outcomes achieved with PCI in the setting of clinical trials may not be reproducible in the real world, mainly because randomized controlled trials usually enroll a select group of patients who are cared for by experts in high-volume centers[9].

Fibrinolytics

Due to its universal availability, fibrinolysis remains the mainstay of reperfusion therapy. Fibrinolytic therapy given early, within 3 hours after symptom onset, can result in mortality reduction of up to 50%[10].

The first fibrinolytic efficiently tested for AMI was streptokinase, showing 18% mortality reduction[11]. In 1993, the GUSTO 1 study demonstrated the superiority of t-PA combined to UFH, over streptokinase, decreasing 30-day mortality rate from 7.2% to 6.3%, with this benefit persisting at one year. T-PA allowed more efficient reperfusion and TIMI grade 3 flows in 54% of the cases[12]. Since then, other studies with newer, fibrin-specific fibrinolytics, such as reteplase (r-PA) and tenecteplase (TNK), represent a small but significant improvement over the first-generation drugs (i.e., streptokinase and urokinase). These new agents can be administered as bolus injections, minimizing time delay in the pre-hospital and emergency room settings. Of the newest fibrinolytic agents, tenecteplase therapy was found to be complicated by fewer major bleeds and blood transfusions than t-PA (4.66% vs. 5.94%, p = 0.0002; 4.25% vs. 5.49%, p = 0.0002, respectively)[13].

In summary, fibrinolysis would be generally preferred for patients with early presentation (< 3 hours from symptom onset), and mainly in the presence of time delay to invasive strategy[9].

PRE-HOSPITAL FIBRINOLYSIS

In select settings, pre-hospital fibrinolysis appears to offer a mortality advantage over in-hospital administration. A meta-analysis of 6 trials with 6,434 patients found a reduction in all-cause hospital mortality (odds ratio 0.83, 95% CI 0.70 - 0.98) with prehospital fibrinolysis[14].

The CAPTIM study randomized patients managed within 6 h of acute STEMI to primary angioplasty or prehospital fibrinolysis (rt-PA) with immediate transfer to a centre with interventional facilities. It found a similar incidence of the primary endpoint of death, recurrent MI, or stroke at 30 days with both strategies[15].

LIMITATION AND HAZARDS OF FIBRINOLYTIC THERAPY

Unsuccessful reperfusion (absence of TIMI 3 flow with first few hours after fibrinolysis) may range from 40% with use of streptokinase to 20%-30% with newer fibrin specific agents[1].

The main hazard remains to be intracerebral bleeding: overall 3.9 strokes per 1,000 patients treated within the first 24h of treatment. Advanced age, female gender, low body weight, hypertension, previous cerebrovascular accident and use of alteplase (r-TPA) constitute risk factors for intracranial hemorrhage[1,3,9].

PRIMARY PCI, TRANSFER AND RESCUE PCI

In patients with STEMI, primary PCI should be treatment of choice in patients presenting to a hospital with a PCI facility and an experienced team, or in the presence of contra-indications for thrombolytic therapy. In cardiogenic shock, emergency PCI may be life saving and should be considered at an early stage. The superiority of PCI over thrombolysis appears to be relevant for the time interval between 3 and 12 hours after onset of symptoms and in high-risk patients (cardiogenic shock, Killip group > 3), based on its capacity of better preservation of myocardium. Within the first 3 hours of symptoms, both strategies are equally effective in achieving reperfusion, reducing MI size and mortality[9].

Trials comparing early (pre-hospital) thrombolysis and transfer to a tertiary center with a PCI facility, observed better clinical outcomes in the group that underwent PCI. However, transfer times caused delays between randomization and start of treatment[14,15].

When thrombolysis fails (less than 50% reduction of ST segment and persistent pain) rescue PCI can be useful when performed within 45-60 minutes after starting the infusion.

FACILITATED PCI

Despite the attractive rational of early administration of a fibrinolytic agent (usually in a low dose)

followed immediately by a more complete mechanical reperfusion by PCI, this strategy has not been able to provide benefit. The recent and early interrupted ASSENT 4 study (TNK facilitated primary PCI vs. primary PCI with Gp IIb/IIIa inhibitor) showed increased number of adverse events in the group of facilitated PCI[16]. At this moment, there is no recommendation to support this strategy[17].

ADJUNCTIVE THERAPY FOR STEMI

Anti-platelet agents have proven themselves to be valuable adjuncts to mechanical reperfusion by reducing these early thrombotic complications. Adjunctive therapy is also important following administration of fibrinolytics. It is thought that fibrin-specific agents, while promoting local clot lysis, may actually exert a systemic pro-coagulant effect through increased thrombin activity and possibly via enhanced platelet aggregation[18,19].

ANTIPLATELET THERAPY FOR STEMI

The ISIS-2 study was the largest trial of aspirin in STEMI; it provides the best evidence that aspirin (ASA) reduces mortality in such patients[20]. ASA should be administered as soon as possible, in 162 – 325 mg doses and continued indefinitely in a lower maintenance dose of 75 to 162 mg. Clopidogrel or ticlopidine are indicated in the presence of true allergy to aspirin[9].

Clopidogrel should be considered in all patients undergoing angioplasty with stent implantation. The Clarity study demonstrated benefits and safety in the use of clopidogrel in patients treated with fibrinolytics and aspirin, showing improved coronary patency by prevention of reocclusion, and decreased adverse event rate[21]. A 300 mg clopidogrel loading dose, followed by 75 mg/day from 1 to 12 months should be used. Patients treated with stents in the acute setting of MI, should take clopidogrel for up to 1-12 months. Those treated with drug elucting stents must take clopidogrel for a longer period of time (more than 6 months). Some specialists consider the use of clopidogrel for indeterminated time based on recent studies that evaluated the risk of late thrombosis[22].

Studies have demonstrated controversial results regarding the use of Gp IIb/IIIa inhibitors in STEM[21,23]. Angiographic and clinical benefits are possible, mainly in the presence of extensive thrombus or in vascular grafts angioplasties. Two recent studies demonstrated no advantage for combination of a thrombolytic agent and a glycoprotein (Gp) IIb/IIIa inhibitor. In patients over 70 years old there was increased risk of bleeding[21,23].

ANTICOAGULATION IN STEMI

Benefit of unfractioned heparin lies in the maintenance of coronary stability in the hours and days following fibrinolytic use. It should be combined to t-PA or TNK for 24-48 hours. The use of low molecular weight heparin is an acceptable alternative in patients under 75 years old and normal kidney function. LMWH should not be used as an alternative to UFH as adjunctive therapy in elderly patients (over 75 years) receiving fibrinolysis. Patients at high-risk of systemic emboli (large or anterior MI, atrial fibrillation, previous embolus, or known left ventricle thrombus) should be given intravenous UFH[9].

OTHER ANCILLARY MEDICATIONS

Beta-blockers are thought to be cardioprotective, reducing infarct size and reinfarction when co-administered with fibrinolytics, and reducing mortality when continued long term after AMI. Oral beta-blockers constitute class I recommendation by the ACC-AHA in the setting of STEMI[9]. Early IV beta-blockers may be considered in special situations such as tachycardia or hypertension[24].

Other medication with class I recommendation are the ACE-inhibitors. These agents limit ventricular dilatation and remodeling by interruption of the renin-angiotensin-aldosterone system. They should be given orally within the first 24 hours post-infarct to patients who have experienced symptoms of heart failure or those known to have left ventricular systolic dysfunction[9].

Angiotensin receptor blocker should be considered as an alternative to ACE-inhibitors in patients with systolic dysfunction (LVEF < 40%) post-MI, as demonstrated by non inferiority of valsartan compared to captopril in the VALIANT study[25].

Long term aldosterone blockade for high-risk patients (LVEF < 40%, heart failure, diabetes mellitus) should be considered[26].

Current guidelines for patients with established coronary artery disease recommend that the goal of treat-

ment should be an LDL cholesterol level of less than 100 mg/dL[4]. However, more aggressive lipid lowering (LDL cholesterol less than 70 mg/dL) further lowers cardiovascular event rates and is safe, although the incremental impact on mortality over moderate lipid-lowering remains to be clearly established[27].

RISK STRATIFICATION AFTER STEMI

Risk stratification of all patients with STEMI begins after the initial event. Patients treated with primary angioplasty may be discharged without additional stratification[9]. Patients treated with fibrinolytics or with no reperfusion treatment, should be investigated according to table 1.

SPECIFIC TREATMENT FOR UA / NSTEMI PATIENTS

Early Risk Stratification

Management of UA/NSTEMI patients requires an early risk stratification to estimate the risk of adverse outcomes (death, infarction, re-infarction, stroke, urgent revascularization and re-hospitalization for ACS). This process is critical to define best therapeutic strategy. Several tools were developed to stratify the risk of these patients: GRACE[28], PURSUIT[29] and TIMI[30] (Table 2) scores and the classification of the American Heart Association/American College of Cardiology[31] (Table 3).

ADDITIONAL PLATELET AGGREGATION INHIBITORS

Several studies have shown that ASA combined with others platelet inhibitors (thienopyridines and glycoprotein IIb/IIIa receptor inhibitors- iGPIIb/IIIa) are beneficial in patients presenting with ACS.
The CURE trial evaluated the efficacy and safety of

Table 1 – Risk Stratification after STEMI[9]

Stratification	Invasive	Noninvasive
Low-risk patients	Optional	Ideal
High-risk patients*	Ideal	Inadequate
Timing	First days	Stress test (sub-maximum or symptom-limited) or imaging test, pre-discharge (5-7days)

*Recurring ischemia, ventricular dysfunction (EF< 40%), positive noninvasive test for ischemia, mechanical complication, hemodynamic or electric instability (sustained ventricular arrhythmias, etc.), previous revascularization or diabetes.

Table 2 – TIMI Risk Score Variables[30]

Age greater than 65 years
Presence of at least 3 traditional risk factors for CAD (male gender, family history, hyperlipidemia, diabetes, smoking, hypertension, obesity)
Prior coronary stenosis > 50%
Use of aspirin within the previous 7 days
Presence of ST-segment deviation on admission ECG
At least 2 anginal episodes in the prior 24 hours
Elevated serum biochemical cardiac markers

• Each variable above is assigned 1 point. Risk score is equal to summation of the points (0-7).
• Patients who obtain a TIMI risk score > 4, and those who fit in the high-risk cohort (AHA/ACC), are the patients that, given the severity of their condition, need more aggressive treatment by early invasive strategy.

Table 3 – Early Risk Stratification in UA/NSTEMI (Risk for Death/MI – One of the described factors is enough to determine the most severe classification – adapted from AHA/ACC[4])

Characteristics	Low-Risk	Intermediate Risk	High-Risk
History		Previous MI peripheral vascular disease, or CABG, prior use of ASA	Accelerating tempo of ischemic symptoms in preceding 48 h
Pain and clinical findings	New episode or progressive pain (CSS CF III or IV*) in the last two weeks, with moderate or high likelihood of CAD	Age = 70-75 years Rest pain > 20 minutes, reversed Rest pain < 20 minutes	Age > 75 years Prolonged ongoing (> 20 min) rest pain Pulmonary edema; B3 or crackles hypotension, bradycardia, or tachycardia. New or worsening mitral regurgitation murmur
ECG changes	Normal ECG	T wave inversions > 0.2 mV Pathological Q waves	Angina at rest with transient ST-segment 0.5 mm depression New or presumed new bundle branch block, Sustained ventricular tachycardia
Biochemical markers CKMB, troponin	Normal	Slightly elevated	Elevated

the combination of clopidogrel plus ASA in 12,562 patients with UA/NSTEMI[32]. This association decreased by 20% the risk of adverse outcomes. Patients undergoing angioplasty with stenting had a 30% risk reduction. Clopidogrel should be administered from 1 to 9 months. Patients undergoing stenting should receive the medication for at least 3-6 months[32].
Previous studies with iGpIIb/IIIa confirmed a substantial reduction on adverse outcomes in high-risk patients with UA/NSTEMI (elevated troponin levels, persistent ischemia, and TIMI risk score > 4). The greatest benefit occurred in patients undergoing angioplasty (risk reduction of AMI or death around 40%). The CAPTURE trial evaluated the efficacy of abciximab in patients with unstable angina. Abciximab was associated with a reduction in 30-day mortality rate, myocardial infarction or urgent revascularization from 15.9% to 11.3%[33]. The PRISM[34] and PRISM-PLUS[35] trials demonstrated a reduction by 43% in the risk of adverse events after UA/NSTEMI (death or non-fatal AMI) within 7 days.

ANTICOAGULATION IN NSTEMI: UFH AND LMWH

A meta-analysis has demonstrated that UFH combined with ASA reduced the risk of death or myocardial infarction by 56% (p = 0.03) after NSTEMI. Medication should be continued for 2 to 5 days or until angioplasty/revascularization[36].
LMWH has increased bioavailability and longer half-life than UFH. Dalteparin and nadroparin were similar to UFH. Enoxaparin was superior to UFH in the ESSENCE[37] and TIMI 11B[38] trials, and is the most used LMWH in UA/NSTEMI. Enoxaparin should be administered in two daily subcutaneous doses of 1 mg/kg for 2-5 days, or until angioplasty.

CHOICE OF HEPARIN FOR COMBINATION WITH GP IIB/IIIA INHIBITOR

At the present time, multiple therapies are used for the treatment of UA/NSTEMI patients. Safety and efficacy of LMWH or UFH combined with iGpIIb/IIIa was recently corroborated. The SYNERGY trial has demonstrated that both UFH and enoxaparin reduced adverse endpoints (death / AMI / myocardial ischemia). Similarly both agents, when combined with GpIIb/IIIa inhibitor and ASA and/or clopidogrel. There were no differences in terms of bleeding[39].

Early Invasive Versus Conservative Strategy

Early invasive strategy consists in performance of cardiac catheterization in the first 24 to 48 hours of presentation. The benefit of this strategy was observed in intermediate-risk and high-risk patients (TIMI > 4 risk score or high-risk in the AHA/ACC classification), with reduction in the adverse endpoints, when compared to conservative strategy. The TACTICS-TIMI 18 study demonstrated that death, non-fatal AMI or re-hospitalization for ACS was reduced from 19.4% to 15.9%[40].
Conservative strategy demands an initial noninvasive evaluation, composed by an echocardiogram for assessment of left ventricular function followed by a cardiac stress test for detection of myocardial ischemia[4].
Intermediate-risk patients may undergo ischemia testing after 48 to 72 hours of stable medical therapy. Cardiac catheterization is strongly recommended for patients with evidence of recurrent ischemia or positive non-invasive test, despite medical treatment[4].
Current guidelines encourage an early invasive strategy in patients with recurrent ischemia, elevated levels of troponin, ST-segment depression, signs of heart failure or mitral regurgitation, ventricular dysfunction (EF < 40%), hemodynamic instability, sustained ventricular tachycardia, and angioplasty within the preceding 6 months or a history of myocardial revascularization[4].

CONCLUSION

The understanding of pathophysiology of ACS and their treatment have evolved substantially over the last decades. Efforts to improve survival in STEMI have focused on reperfusion strategies. Early diagnosis and risk stratification have been considered the cornerstone of management for patients with UA / NSTEMI.

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