

Guidelines of the Brazilian Society of Cardiology for Unstable Angina and Non-ST Segment Elevation Acute Myocardial Infarction

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Note: These Guidelines are intended to inform and not to substitute the physician's clinical judgement which ultimately should determine the appropriate treatment for his/her patients.

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Declaration of a potential conflict of interests of authors/collaborators of the Guidelines for Unstable Angina and Non-ST Segment Elevation Acute Myocardial Infarction (2nd Edition, 2007)

If in the last three years the author/collaborator of the guidelines

	Participated in clinical and/or experimental studies funded by pharmaceutical industry or equipment industry, whose use is related to these guidelines	Participated as a speaker in meetings or other activities sponsored by the industries related to these guidelines.	Participated as a member of the consultant council or directing council in pharmaceutical or equipment industry	Participated in normative committees of scientific studies sponsored by the industry	Received personal or institutional grants from the industry	Elaborated scientific texts for publications sponsored by the industry	Owens industry stocks
José Carlos Nicolau	Astra-Zeneca, Bayer, BMS, J&J, GSK, Lilly, MSD, Pfizer, Schering Plough, Sanofi-Aventis	BMS, Sanofi-Aventis	Astra-Zeneca, Lilly, Sanofi-Aventis	no	Astra-Zeneca, Pfizer, Schering-Plough, Sanofi-Aventis	BMS	no
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DEFINITIONS OF RECOMMENDATIONS AND EVIDENCES

Recommendations

- **Class I:** Conditions for which there are conclusive evidences or, in case of their absence, a general consensus that the procedure is safe and useful/efficacious.
- **Class II:** Conditions for which there are conflicting evidences and/or divergences of opinion on safety and usefulness/efficacy of the procedure.

Class IIa: Weight or evidence/opinion in favor of the procedure. The majority approves.

Class IIb: Less well-established safety and usefulness, with no preponderance of favorable opinions.

- **Class III:** Conditions for which there are evidences that the procedure is not useful/efficacious and, in some cases, may be harmful.

Evidences

- **Level A:** Data obtained from multiple randomized studies of good size, which are in agreement and/or have a sound meta-analysis of randomized clinical studies.
- **Level B:** Data obtained by less sound meta-analysis, from a single randomized study or from not randomized (observational) studies.
- **Level C:** Data obtained from consensual opinions of specialists.

Note: drugs not commercialized in Brazil (in spite of being included in the text of the document) are not included in the recommendations.

Part 1

Risk stratification and management in the first 12 hours after the patient's arrival at the hospital

Introduction

In the United States unstable angina (UA) is the most common cardiovascular cause of hospitalization being also responsible for most hospital confinements in coronary units¹. During their evolution, a part of these patients develops increases in biochemical markers of myocardial damage, taking the shape of an acute non-ST segment elevation myocardial infarction (NSTEMI). These two entities (UA and NSTEMI), as a whole form the non-ST segment elevation acute coronary syndromes (ACS), the object of these Guidelines. The patient with UA has a variable prognosis regarding unfavorable events such as acute myocardial infarction (AMI), death, recurrent angina and need for myocardial revascularization². Due to the wide variation of clinical manifestations of these non-ST segment elevation ACS their risk stratification helps to determine strategies for ambulatory or in-hospital treatment³, allowing to adequate costs in function of a greater therapeutic efficacy^{4,5}.

1. Clinical history and physical examination History of present disease

The clinical history of the patient with a non-ST elevation ACS plays an important role in the risk stratification. The mostly used UA classification is that proposed by E. Braunwald^{6,7}. Its prognostic and therapeutic value has been validated by numerable prospective clinical studies, therefore reaching a high degree of acceptance^{8,9}. It takes into account the severity of the angina symptoms, the clinical circumstances of their occurrence and the intensity of the used treatment (Table 1). The same author also proposed a classification based on clinical criteria, according to which the patients are divided into subgroups of high, intermediate and low risk for death or non fatal AMI⁷ (Table 2). Braunwald's classification evidences the difference in the prognosis of patients according to the subgroup to which he/she belongs⁶. However, some of these criteria are not sufficiently supported by clinical evidences available in the literature, difficulties occurring also from the practical viewpoint for the inclusion of some patients in certain subgroups. Some studies did not find a

good correlation between the different subgroups and risk estimates for major cardiac events¹⁰. Van Miltenburg et al.⁹ observed 417 patients with UA and followed them up for six months. Death and AMI occurred more frequently in the subgroups of recent onset angina and pain on rest, and in the patients with post-infarction angina (Class C). In this study, Class C patients had a significantly shorter (80%) survival when compared to Classes A (97%) and B (89%). An infarction-free survival or need for intervention was greater in Class II (72%), intermediate in Class I (53%) and lower in Class III (35%). Presence of electrocardiographic alterations, need for maximum anti-anginal therapy and presence of recurrent or refractory ischemia are also independent risk factors for a poor prognosis. In the ECLA III study¹¹, refractory angina was the most important independent prognostic factor for infarction and death. The patients who obtained relief of angina after hospitalization constituted a very low-risk subgroup. In this subgroup the incidence of AMI and death were, respectively, 1.8% and 1.5%; on the other hand, in the patients who evolved with refractory angina after adequate clinical treatment, AMI and death incidences were, respectively, 1.5% and 1.4%. In the GUSTO IIB trial¹², of the analyzed 3,513 patients with non-Q-wave AMI 36% evolved with recurrent ischemia with 70% responding to clinical treatment. In a 30-day follow-up those with refractory ischemia presented 29% and 16% incidence of reinfarction and death, respectively. In the subgroup with recurrent ischemia responsive to clinical treatment these incidences were 12% and 6%; and in the subgroup that did not present ischemia the incidences were 3% and 4.3%, respectively. In this trial 4,488 patients with UA were included. Of these, 14% had recurrent ischemia with 82% of them responding to clinical treatment. AMI incidences within up to 30 days in the subgroups with recurrent refractory ischemia, with ischemia responsive to clinical treatment and without recurrent ischemia were 22%, 7.2% and 2.3%, respectively. And death incidences were 8.2%, 2.9% and 1.6% respectively. The most sensitive biochemical markers of myocardial lesions such as troponins brought support for the diagnosis and prognosis of non-ST segment elevation ACS leading to an adaptation of the original Braunwald classification adopted by the North-American

Guidelines. As can be observed in Table 3, the fundamental alteration occurred in group IIIB which was subdivided into troponin-negative and troponin-positive. Obviously the troponin-positive subgroup IIIB presents a worse diagnosis in relation to that with negative troponin^{13,14}. In UA, risk factors for adverse events include age, continuous pain at rest, intracoronary thrombi¹⁵, diabetes mellitus⁴ and complex coronary or multiple vessel lesions. Based on analysis of a data bank of the TIMI 11B study, Antman et al.¹⁶ found the following independent markers of worse prognosis in patients with non-ST elevation ACS ("TIMI group risk score"): age ≥ 65 years, increase in biochemical markers; ST-segment depression ≥ 0.5 mm, use of ASA during the last 7 days; presence of 3 or more traditional risk factors for coronary artery disease (hypertension, hypercholesterolemia, diabetes mellitus, smoking, family history); known coronary artery disease; severe angina of recent onset (< 4 hours). Giving one point for each of these items, the patient is categorized as: low risk (0–2 score), intermediate risk (3–4 score) or high risk (5–7 score). This "risk score" was validated in other ACS studies of non-ST segment elevation ACS, observing in all of them an increase in the incidence of events (death, reinfarction and recurrent ischemia requiring revascularization) in direct proportion with increase in risk score.

UA in the elderly

WHO establishes that in developing countries an individual is considered elderly when 60 or more years old and in developed countries when 65 or more years old.

Table 1. Braunwald classification for unstable angina⁷.

1. Severity of symptoms

Class I – Angina of recent onset (less than 2 months), frequent or very intense (3 or more times a day), accelerated (evolutionally more frequent or in consequence of progressively less efforts)

Class II – Rest angina or subacute angina (1 or more episodes at rest in the last 30 days, with the last episode occurring more than 48 hours ago)

Class III – Acute angina at rest (one or more episodes at rest in the last 48 hours)

2. Circumstances of the clinical manifestations

Class A – Secondary unstable angina (anemia, hyperthermia, hypotension, uncontrolled hypertension, unusual emotions, aortic stenosis, arrhythmias, thyrotoxicosis, hypoxemia, etc)

Class B – Primary unstable angina

Class C – Post-infarction angina (more than 24 hours and less than 2 weeks)

3. Treatment intensity

Class 1 – Without or with minimal treatment

Class 2 – Usual anti-anginal treatment

Class 3 – Maximal therapy

Cardiovascular diseases present expressive morbidity and mortality in the elderly population. In the United States, the elderly correspond to 13% of the population, however, they are responsible for 65% of the hospitalizations due to cardiac disease. Approximately 85% of the deaths due to AMI occur in the elderly population^{17,18}. Up to 65 years, coronary artery disease (CAD) is much more prevalent in

Table 2. Risk stratification in unstable angina⁷.

High risk	Intermediate risk	Low risk
At least one of the following findings has to be present:	No high risk finding, but should have any of the following:	No high or intermediate risk finding but should have any of the following:
Prolonged and lasting pain at rest (> 20 minutes)	Absent angina at rest at the moment of evaluation, but without low probability of CAD	Angina with increasing frequency, severity or duration
Lung edema	Angina at rest (> 20 minutes) or improving with rest or nitroglycerine	Angina in consequence of low effort threshold
Angina associated with mitral insufficiency murmur	Nocturnal angina	Angina of recent onset at an interval from 2 weeks to 2 months
Angina with 3 rd sound on cardiac auscultation or stertors	Angina of recent onset Class III or IV (CCS) in the last two weeks but with a low probability of CAD	Normal or unaltered electrocardiogram
Angina with hypotension	Q waves or ST depression ≥ 1 mm in various leads Age > 65 years	
Angina at rest with dynamic ST (> 1 mm) alterations	Angina with dynamic T-wave alterations	

CAD = coronary artery disease; CCS = Canadian Cardiovascular Society.

Table 3. Stratification of risk for death or infarction in patients with non-ST elevation acute coronary syndrome¹⁴.

Characteristics	High	Moderate	Low
History	Age >75 years Progressive pain, symptoms in the last 48 hours	Age 70-75 years Previous infarction, peripheral vascular disease, diabetes mellitus, revascularization surgery, previous use of ASA	
Precordial pain	Prolonged (>20 min) at rest	Prolonged (>20 min.) at rest but with spontaneous relief or by nitrate	New angina symptoms CCS class III or IV in the last two weeks without pain during prolonged rest (>20 min.)
Physical examination	Lung edema, worsening or emergence of mitral regurgitation murmur, B3, hypotension, bradycardia and tachycardia		
Electrocardiogram	ST-segment depression >0.5 mm (associated or not with angina), dynamic ST alteration, new or presumably new bundle branch block, sustained ventricular brachycardia	T wave inversion >2 mm, pathologic Q waves	Normal or unaltered during the episode of pain
Serum ischemia markers	Markedly elevated	Slight elevation	Normal

*TnIc, TnTc or CK-MB (preferably mass) elevated = above 99th percentile; slight elevation = above detection level and below 99th percentile. CCS = Canadian Cardiovascular Society

men and from 80 years on its prevalence is equivalent in both genders. The elderly with non-ST elevation ACS in general present a different risk profile from that of the non-elderly: they have a higher prevalence of arterial hypertension, diabetes mellitus, previous myocardial infarction, angina, peripheral vascular disease, cerebrovascular disease (stroke), multiarterial disease and heart failure. On the other hand, they present lower cholesterol levels and lower smoking prevalence. Generally the elderly person looks for medical assistance later after onset of symptoms. Regarding non-ST elevation ACS, instead of pain, frequently they present the so-called "ischemic equivalents" such as dyspnea, indisposition, mental confusion, syncope or lung edema. In addition, in relation to the non-elderly they have a lower elevation of cardiac enzymes and higher occurrence of non-Q-wave AMI¹⁹. Regarding non-ST elevation ACS, the elderly present a higher incidence of complications which implies the need for more intensive treatment. However, especially in those over 75 years, frequently the most applied therapy with betablocker, ASA, anticoagulant and hypolipidemic drugs is not used. Still less used in the elderly are thrombolytic therapy and revascularization through angioplasty or surgery^{20,21}. In the registry of the TIMI III study²² with 3,318 patients with UA and non-Q-wave AMI, 828 patients were over 75 years old. These individuals received anti-ischemic therapy and,

at a lower proportion than the younger ones, were submitted to coronary angiography. And despite presenting more severe and extensive CAD they were less frequently submitted to myocardial revascularization procedures and had more adverse events in up to six weeks of evolution.

Former history

Patients submitted to procedures (angioplasty with or without stent and or coronary artery bypass graft - CABG - surgery)

Recurrence of angina after CABG or percutaneous intervention may suggest development of acute complications, new lesions, late in-stent thrombosis or restenosis. Chest pain up to 48 hours after percutaneous intervention is indicative of acute obstruction, transient coronary spasm, non occluding thrombus, branch occlusion or distal embolization. Recurrent chest pain until six months of the procedure probably is more related to restenosis; on the other hand, onset of angina after this period usually is related to a new coronary lesion. In the case of CABG, the early onset of pain usually is associated with thrombotic obstruction of the graft; from the first month to the first year post-CABG, the mechanism usually relates to fibrous hyperplasia of the intima; after this period, it is indicative of a new atherosclerotic lesion and/or non-thrombotic graft degeneration. Therefore, in the patients with symptoms suggestive of UA

who have already been submitted to myocardial revascularization, especially in those who present with pain on rest, interventional approach is indicated. The TIMI III registry compared the incidence of death and non-fatal infarction among patients who presented UA and non-Q-wave infarction with or without previous CABG. The patients with previous CABG had higher complication rates both in the analysis up to 10 days after admission (4.5% in the group with previous CABG vs. 2.8% in the group without CABG) and in the analysis after 42 days (7.7% vs. 5.1%, respectively)²³.

Risk factors for CAD

Although the presence of risk factors such as systemic arterial hypertension, diabetes mellitus, dyslipidemia, family history and smoking are associated with a higher probability of CAD, there is no well-defined correlation of its importance for clinical evolution in patients admitted with non-ST elevation ACS. In some studies there are also paradoxical observations indicative of a better evolution among smokers^{24,25}. On the other hand, Antman et al.¹⁶ demonstrated that the presence of 3 or more factors constitute an independent marker of worse prognosis.

Physical examination

Usually physical examination in the context of non-ST elevation ACS is little expressive. Indeed, it can be said that a normal physical examination is the rule for a situation of non-ST elevation unstable angina and AMI. The initial evaluation of the patients consists of a general physical examination with measurement of blood pressure and heart rate. Usually the patient with pain due to coronary insufficiency is tense, restless, with face expressing pain, often with diaphoresis and tachypnea. Patients complaining of precordial pain and at ease, talking freely and without signs of discomfort, have not the most adequate substrate to value a hypothesis of non-ST elevation ACS. As a rule, the isolated evaluation of a physical examination, either normal or with slight alterations, is insufficient for risk stratification because even patients with multiaarterial lesions or lesions of the left main coronary artery may present a normal physical examination^{6,26-28}. However, when present, the alterations of the physical examination may present important implications in the patient's categorization as high risk. Among these markers of a poor prognosis, the following are to be noted:

1. Presence of mitral murmur, holosystolic or not, transient or not, with or without irradiation, with normo- or hypophonetic first sound. Verification of murmur during painful episodes or intensification of a preexisting murmur greatly reinforces the diagnosis of ischemia or even papillary muscle rupture. When there is papillary muscle rup-

ture with mild mitral insufficiency, usually the initial clinical control is achieved and the mitral insufficiency itself tends to regress. However, the presence of papillary muscle rupture with severe mitral regurgitation represents a dramatic situation demanding an immediate invasive stratification. Anyhow it is well demonstrated that the presence of a new mitral insufficiency, or the worsening of an already preexisting one, is a marker of poor prognosis in patients with non-ST elevation ACS^{29,30}.

2. Presence of tachycardia (heart rate above 100 bpm), tachypnea, hypotension, diaphoresis, weak pulses, third sound and pulmonary rales during painful episodes indicate severe myocardial impairment leading to cardiac failure and also select a high-risk population. In case of doubt, physical examination is useful not only in risk stratification, but also in the diagnosis of non-ST elevation ACS itself. Thus the presence of uni- or bilateral carotid murmur, decrease of peripheral pulses, xanthelasma or xanthoma and presence of abdominal aorta aneurism reinforce the diagnosis of atherosclerotic coronary artery disease. On the other hand, presence of pericardial friction suggests acute pericarditis, pleural friction suggests embolism with pulmonary infarction, decrease in vesicular murmur suggests pneumothorax, pulse asymmetry and/or aortic insufficiency suggest dissection of the aorta, clicks or mitral meso-telesystolic murmurs suggest mitral valve prolapse, parasternal ejection murmur suggests hypertrophic cardiomyopathy, and giant A wave and hypertrophic second sound suggest pulmonary arterial hypertension.

Clinical history and physical examination

Summary of recommendations and evidences

RECOMMENDATION CLASS I

- All patients should be evaluated and classified into high, intermediate or low probability of presenting non-ST elevation ACS (Table 4) (*level of evidence: B*).
- All patients should be stratified and classified into high, intermediate or low risk of developing major cardiac events (Table 3) (*level of evidence: B*).

2. Previous use of drugs

Previous therapy seems to influence the evolution and therapeutic response of patients admitted due to non-ST elevation ACS. Admitted patients using acetylsalicylic acid previously present more frequently the final diagnosis of unstable angina than the diagnosis of acute myocardial infarction and evolve with less infarction area and without development of Q wave³¹⁻³³. In the phase of registry of the TIMI (Thrombolysis in Myocardial Ischemia) III study it was observed that, in spite of the high prevalence of previous

Table 4. Probability of signs and symptoms being due to unstable myocardial ischemic syndromes secondary to obstructive coronary disease.

Variables	High probability	Intermediate probability	Low probability
History	Symptoms suggestive of prolonged myocardial ischemia (>20 minutes) at rest, or signs of previous anginal state. History of CAD, including AMI	Symptoms suggestive of myocardial ischemia as main manifestation. Age >70 years. Diabetes mellitus. Peripheral vascular disease	Symptoms not suggestive of myocardial ischemia. Recent use of cocaine
Physical examination	Transient mitral insufficiency, hypotension, diaphoresis, lung edema or rales		Thoracic discomfort, reproduced by palpation
ECG	New or presumably new ST-segment depression (>0.5 mm), or >2 mm T-wave inversion with symptoms	Presence of Q waves. Old abnormal ST-segment or T-waves	T-wave flattening or T-wave inversion in leads with predominant R waves. Normal ECG
Biochemical markers	Elevated TnT, Tnl or CK-MB	Normal markers	Normal markers

CAD=coronary artery disease; AMI=acute myocardial infarction; ECG=electrocardiogram; TnT=troponin T; Tnl=troponin I.

coronary arterial disease in patients admitted due to unstable angina or non-ST elevation AMI, only 45% of the patients used ASA and 27% used betablockers, while nitrates and calcium channel blockers were used by approximately 45% of the patients. In a multivariate analysis, the previous use of nitrates was correlated with a 1.6 times higher risk for death or myocardial infarction in the first subsequent year (95% CI=1.16–2.20; $p=0.004$)³⁴. However, in the TIMI III study, in spite of the fact that the women received nitrates, betablockers and calcium channel blockers with a greater frequency and less aspirin, their evolution was similar to that of the men and was correlated only with other markers of disease severity³⁵. In a multivariate analysis of the PURSUIT study, the subgroups in previous use of betablockers, calcium channel blockers or nitrates presented a 15% to 40% higher relative risk for death or death + non fatal myocardial infarction when compared with patients who did not use these drugs. Patients with previous angioplasty presented a better survival but the opposite occurred with those submitted to myocardial revascularization surgery³⁶. This same type of interaction was observed in the PRISM-PLUS study. Previous revascularization surgery increased 46% and angioplasty decreased by 32% the incidence of residual thrombus after tirofiban infusion, the beneficial tirofiban effect being significantly greater among the patients in previous therapy with betablockers. A trend to better evolution was also observed among users of acetylsalicylic acid^{37,38}. On the other hand, on a retrospective analysis of the TIMI IIB and ESSENCE studies it was observed that the previous use of acetylsalicylic acid and betablockers represented an important risk factor for ischemic events¹⁶.

Summary

The previous use of acetylsalicylic acid is a factor of major severity in patients with suspicion or a confirmed diagnosis of unstable non-ST elevation ACS.

The previous use of betablockers, nitrates and calcium channel blockers is associated with worse evolution.

Note: obviously these data do not indicate that these drugs should not be used. They only signal is that if clinical instability occurred despite their previous use, the underlying conditions usually are more severe.

3. Electrocardiogram

Autopsy data demonstrated that ECG has not sufficient sensitivity and specificity to allow a reliable distinction between transmural and subendocardial infarction, since patients with transmural infarction may not develop Q waves, and Q waves may be seen in patients with an autopsy finding of subendocardial (not transmural) infarction³⁹. However categorization of patients into groups with Q waves and without Q waves based on ECG is useful, because AMI with Q waves are usually associated with greater myocardial damage, higher tendency to expansion and remodeling of the infarct area, and consequently, higher mortality⁴⁰. Q wave in ECG means abnormal electric activity but is not a synonym of irreversible cardiac damage. On the other hand, absence of Q wave may simply reflect the lack of conventional 12-lead ECG sensitivity, especially in the posterior left ventricle wall. In cases of subendocardial AMI confirmed at autopsy, ST-segment depression and/or alterations in T wave are observed in only 50% of the cases⁴¹. In non-ST elevation AMI a higher inci-

dence of subtotal obstruction of the guilty coronary vessel and a greater collateral flow to the infarcted area is observed. In addition, the patients are on average older and present a higher incidence of previous AMI³⁹. ST-segment and T-wave alterations are not specific and may occur in a series of conditions which include: stable and unstable angina, ventricular hypertrophy, acute and chronic pericarditis, myocarditis, early repolarization, electrolytic alteration, shock, metabolic disorder and digitalis effect. Serial ECG may have a considerable value in the differentiation of these conditions with non-Q-wave AMI. Transient alterations favor angina and electrolytic disorders, while persistent alterations favor AMI if other causes such as shock, digitalis or metabolic disorders may be discarded. Ultimately, non-transmural AMI diagnosis is based more on the combination of clinical findings and on elevation of serum enzymes than on ECG. Patients with non-Q-wave AMI may present ST-segment depression, T-wave inversion or even a 12-lead ECG without a well-defined abnormality.

Unstable angina (UA)

Transient ST-segment deviations (depression or elevation) and T-wave inversion occur usually, but not always, in UA. Dynamic ST-segment alterations (ST depression or elevation) or T-wave inversions during an episode of pain, which resolve at least partially when symptoms are alleviated, are important markers of adverse prognosis, that is, subsequent AMI or death⁴². A subtle and infrequent electrocardiographic manifestation of UA is the presence of a transient inverted U wave⁴³. Patients with ST alterations in anteroseptal leads frequently present a significant stenosis of the anterior descending coronary artery and constitute a high-risk group⁴⁴. Diagnostic accuracy of an abnormal ECG increases when a previous ECG tracing is available for comparison. In general, these ECG alterations reverse completely or partially on pain alleviation. Persistence of these alterations for more than 12 hours may suggest non-Q-wave AMI. If the patient has a previous typical history of stable angina or established CAD (previous AMI, angiographic documentation of coronary lesion or previous positive treadmill test), UA diagnosis may be based on the presence of clinical symptoms even in the absence of electrographic alterations. It is in the subgroup of patients without CAD evidences and without ECG alterations associated with pain that the diagnosis becomes more difficult.

Continuous ECG monitoring

Ischemic chest pain is not a reliable or sensitive marker of acute transient myocardial ischemia. Episodes of primary coronary flow reduction may be associated with variable and minimal ECG alterations which precede symptoms

of pain and discomfort. Before the wide use of ASA and heparin it was seen through continuous ECG monitoring that 60% of the patients with UA presented asymptomatic episodes of segment-ST depression⁴⁵. These episodes decreased 5% and 20% in more recent years with the use of ASA and heparin⁴⁴. The presence of ischemia on Holter is an excellent marker of unfavorable clinical evolution, both in the long and the short term⁴⁶⁻⁴⁸.

Prinzmetal's variant angina

The most characteristic data for the diagnosis of variant angina are segment-ST elevation in the presence of pain and regression of elevation on symptom alleviation. In some patients, ST-depression episodes may follow the ST-elevation episodes and are associated with T-wave alterations. Alternation of ST-segment and T wave is the result of ischemic delay in stimulus conduction and may be associated with potentially lethal ventricular arrhythmias. On the other hand, R-wave growth may be associated with the occurrence of ventricular arrhythmias⁴⁴. Many patients show multiple episodes of asymptomatic ST-segment elevations (silent ischemia). ST-segment deviations may be present in any lead. The concomitant presence of ST-elevation in anterior and inferior leads (reflecting extensive ischemia) is associated with a higher risk for sudden death⁴⁴. Transient disorders of stimulus conduction may occur during ischemia episodes. Ectopic ventricular activity is more common during longer ischemic episodes and often is associated with ST-segment and T-wave alterations, being related to a worse prognosis. Rouan et al.⁴⁸ demonstrated that patients with an initial normal ECG or one with minimal and non-specific alterations presented 3% AMI and 6% mortality rates which rise to 12% in patients with an already initial evidence of AMI in ECG. Of the 1009 patients with AMI, 80% presented Q wave, new ST-segment alteration or T-wave inversion and 10% presented left bundle branch block or pacemaker (PM) rhythm making the electrographic diagnosis difficult. The remaining 10% had a normal ECG or one with minimal non-specific alterations. These data support Brush et al's study⁴⁹ where complications with risk for death in patients with evidence of infarction, ischemia, LV hypertrophy, left bundle branch block or PM rhythm was 23 times higher in relation to patients with normal ECG or one with non-specific alterations. New and more sophisticated methods of acquisition and computed interpretation of ECG improved this method's usefulness in accessing the electric cardiac signal⁵⁰.

Serial 12-lead ECG

Approximately 50% of the patients with AMI evaluated at an emergency room present a normal 12-lead ECG or

a non-diagnostic one. During the initial hospitalization period approximately 20% of these patients develop consistent alterations with transmural lesion. Thus, the ideal in this initial phase is to perform serial electrocardiograms. Through serial ST monitoring analyzing (angiographically proven) criteria of reperfusion on ECG, Krucoff et al.⁵⁰ demonstrated an 80% sensitivity and 82% specificity. Another way to measure the electric cardiac wave consists of using 22 surface electrodes and a computer program to evidence signal variation in each lead by high frequency sample. With this methodology, Justis and Hession⁵¹ noted that patients with ischemia due to partial coronary occlusion seem to have an electric wave variability emanating from the affected myocardium. Sensitivity for AMI was 83% as compared with conventional ECG, while specificity was reduced to 76%, as compared with the 99% of the conventional ECG.

Prognosis

In the GUSTO II study the ECG presented by the patients with non-ST elevation ACS was of prognostic importance regarding early mortality⁴⁷.

Left bundle branch block, left ventricular hypertrophy or PM rhythm evolved with 11.6% mortality; ST-segment depression with 8%; ST-segment elevation with 7.4%; and T-wave inversion or normal ECG with 1.2%. In the TIMI III registry supplementary study³⁹, in 1,416 patients with UA or non-Q-wave AMI the following forms of ECG presentation were observed: ST-segment deviation ≥ 1 mm in 14.3%;

left bundle branch block in 19%; isolated T-wave inversion in 21.9% and absence of these alterations in 54.9%.

The following conclusions were reported: patients with UA and ST-segment deviation ≥ 1 mm had a worse prognosis; patients with ST deviation ≥ 1 mm were older; patients with isolated T-wave inversion had characteristics similar to those without ECG alterations; multi-arterial disease was found in 66% of the patients with ST alterations as compared with 40% in those without ECG alteration ($p < 0.001$); absence of significant coronary stenosis ranged from 10% in patients with ST alterations to 29% in patients without ECG alterations and 34% in patients with left bundle branch block (LBBB); non-q-wave AMI incidence ranged from 19% in patients without initial ECG alterations to 29% in patients with ≥ 1 mm segment-ST alterations ($p < 0.001$); in the LBBB patients, instead, it was 32%, and 31% in those with isolated T-wave inversion, the general mean being 24.8%; in-hospital mortality was 1% and from 2% to 5% in 42 days, increasing to 9.8% in one year in the patients with ST ≥ 1 mm alterations as compared with a 5.5% mortality in the patients with T-wave alterations or without ECG alterations ($p < 0.001$) (Tables 5 and 6).

Degrees of ST-segment alteration and follow-up (Table 7)

A total of 187 patients (13% of the whole group) had ST-segment alterations equal to or greater than 0.5 mm³⁹. The clinical outcomes were similar or even worse for pa-

Table 5. ECG and in-hospital outcomes¹².

Factors	All N (1416)	LBBB N (127)	ST ≥ 1 mm N (202)	Isolated T-wave alteration N (310)	Without ECG alteration N (777)	p of the four	ST alteration - (+ or -)
Coronariography performed	62.4	45.4	66.6	65.6	62.5	0.003	0.03
0 vessel disease	24	33.5	10.4	16.7	29.1		
1 vessel disease	30.1	29.6	23.3	32.9	30.7	<0.001	<0.001
2 vessel disease	22.2	14.7	32.7	25.8	19.1		
3 vessel disease	23.7	22.2	33.9	24.6	21.1		
Left main disease	7.4	4.7	15.3	7.6	5.7	0.016	0.019
PTCA	20.3	5.8	23.5	22.4	20.6	0.045	0.582
CABG	11.5	7.6	21.8	14.6	8.7	<0.001	<0.001
In-hospital event							
Death	0.6	0.3	1.4	1.0	0.4	0.112	0.033
AMI	1.4	0.4	1.7	1.3	1.5	0.4	0.3
Death or AMI	1.8	0.8	2.6	1.6	1.6	0.2	0.09
Ischemia with altered ECG	9.5	5.6	18.2	11.4	7.5	<0.001	<0.001
Death/AMI/altered ECG	10.5	6.4	20.2	12.6	8.3	<0.001	<0.001
Ischemia without alteration in ECG	31.6	37.0	31.2	31.6	31.0	0.3	0.93

Table 6. Events in 42 days and in 1 year¹².

	All patients (n=1416)	LBBB (n=127)	ST Alt >1 mm (n=202)	Isolated T-wave alteration (n=310)	Without ECG alteration (n=777)	p	
						Four ways	ST-segment alteration x without ST-segment alteration
42 days							
Death	2.4	5.2	2.5	2.8	1.8	0.198	0.091
AMI	2.2	1.8	1.5	2.4	2.3	0.725	0.41
Death or AMI	4.0	6.6	3.6	3.7	3.7	0.443	0.123
Rehospitalization due to angina	5.3	6.7	7.3	5.6	4.5	0.13	0.032
Death/AMI/recurrent ischemia	16.1	14.2	23.6	17.9	13.9	<0.001	<0.001
PTCA	20.7	3.4	24.9	23.9	20.4	0.024	0.538
CABG	13.4	10.5	25.8	16.3	10.7	<0.001	<0.001
PTCA or CABG	33.4	12.6	50.8	39.3	30.4	<0.001	0.001
1 year							
Death	7.2	18.2	9.8	5.6	5.5	<0.001	<0.001
AMI	4.0	6.3	6	3.7	3.5	0.446	0.13
Death or AMI	9.5	22.9	11	6.8	8.2	<0.001	0.001
Rehospitalization due to angina	15.9	13.4	17.7	16.8	15.4	0.753	0.293
Death/AMI/recurrent ischemia	28.3	34.0	36.1	30.4	25.5	0.003	0.001
PTCA	22.9	7.6	25.3	26.2	22.8	0.037	0.621
CABG	16.1	10.8	27.2	17.9	14.3	0.004	0.002
PTCA or CABG	36.4	16.6	51.1	42.3	33.9	<0.001	0.001

Table 7. Degree of ST deviation and evolution¹².

	Degree of ST deviation				p
	> 2 mm (n=63)	1 mm (n=139)	0.5 mm (n=187)	None (n=900)	
Death within 42 d	0.8	3.0	7.1	1.1	0.002
Death or AMI 42 d	2.8	3.4	10.7	2.4	0.001
Death/AMI/Recurrent ischemia 42 d	19.5	22.7	25.8	13.0	<0.001
Death or AMI in 1 year	14.9	9.7	16.3	6.1	<0.001

tients with 0.5-mm deviated ST-segment as related to those with deviation ≥ 1 mm.

Multivariate analysis (Table 8)

Seven variables were identified as independent prognostic factors for death or AMI in 1 year. The two variables related to ECG were LBBB and ST deviation ≥ 0.5 mm (Table 4). In another model ST deviation ≥ 1 mm was an independent factor but had a lower discriminating power in relation to the 0.5 mm deviation. Using the LBBB criterion or ST alteration ≥ 0.5 mm, death or AMI rate in 1 year was 15.8%. The Minnesota code was not used in this study because it was deemed complex and without

clinical application. On the other hand, patients with AMI with ST-segment depression represented 11% of the cases in Mahon et al's study⁵². In this study the Minnesota Code was used. The patients with ST-segment depression were older in relation to the remainder of the group and presented a higher prevalence of previous AMI (40% vs 25%) and multiarterial disease (71% vs 47%). The group with ST depression presented higher in-hospital mortality (31% vs 17%, $p < 0.01$) and after 36 months (56% vs 32%, $p < 0.001$). Cohen et al.^{53,54} observed in patients with Q-wave AMI and UA that depression of ST-segment had a prognostic value for death or AMI. Farkouh et al.⁵⁵, comparing 424 patients admitted to a chest pain unit with hos-

Table 8. Multivariate Analysis. Prognostic factors (Death or AMI in 1 year in 1,411 patients)¹².

Characteristics	OR (95%CI)	P
Age (decade)	1.43 (1.26-1.61)	<0.001
Thrombolysis-previous week	9.40 (2.94-30.01)	<0.001
LBBB	2.80 (1.81-4.32)	<0.001
ST >0.5 mm	2.45 (1.74-3.45)	<0.001
Other major disease	1.94 (1.33-2.84)	<0.001
TIMI IIIb exclusion	5.61 (1.74-18.06)	0.004
Nitrate – previous week	1.60 (1.16-2.20)	0.004

pitalized patients did not observe significant differences of ECG findings between the two groups.

Arrhythmias

A patient with tachycardia (rate above 100 bpm) and with bradycardia (heart rate <50 bpm) has a worse prognosis. Extrapolating GUSTO I study data, in patients with Q-wave AMI⁵⁶, atrial fibrillation, although not common in AMI, is a marker of worse prognosis. Tachycardia and ventricular fibrillation (VF) occur in up to 20% of the patients with AMI and both are associated with worse prognosis. In the GUSTO I study, 10.2% had sustained ventricular tachycardia, VF or both. Older age, arterial hypertension, previous AMI, anterior wall AMI and decreased ejection fraction were associated with a higher risk for sustained ventricular tachycardia and VF. These ventricular arrhythmias were associated with higher in-hospital mortality in 30 days and in one year follow-up⁵⁷.

Electrocardiogram

Summary of recommendation and evidences

RECOMMENDATIONS CLASS I

- All patients with non-ST elevation ACS or suspicion of non-ST elevation ACS should have an electrocardiogram (ECG). Ideally the ECG should be performed in up to ten minutes after the patient's arrival at the hospital (*level of evidence: B*).
- ECG should be repeated at least once within 6 hours in non diagnostic cases (*level of evidence: C*).

Obs.: In the presence of a previous electrocardiogram, this should be used for comparison. Any new or presumably new alteration of the ST-segment or T-wave is associated with a greater chance of coronary disease. Presence of ST depression >0.5 mm is associated with high risk for cardiac events in patients with non-ST elevation ACS. Individuals with T wave inversion >2 mm or pathologic Q waves present an intermediate risk for events. Dy-

namic ST-segment alterations (ST depression or elevation ≥ 1 mm, and/or T-wave inversion which resolve at least partially when symptoms are alleviated are markers of adverse prognosis.

Arrhythmias – Tachycardia (HR >100 bpm), bradycardia (HR <50 bpm) or complete new or presumable new branch block are markers of worse prognosis. Presence of pathologic new or old Q waves in the ECG imply in intermediate risk.

Continuous ECG monitoring – Whenever possible continuous ECG monitoring is recommended in the emergency room during the period of observation of the patient with suspicion of acute coronary disease.

4. Biochemical markers of myocardial lesion

Biochemical markers are useful to help both in the diagnosis and the prognosis of patients with non-ST elevation ACS. Traditionally total creatine kinase (CK) and lactate dehydrogenase (LDH) were measured. However, at present other biochemical markers, protein constituents of the muscle cell and without enzymatic function have also been used with this purpose. The set of these macromolecules released to the blood stream has been called biochemical markers of myocardial lesion. When myocardial cells are irreversibly damaged their cell membranes lose integrity, the enzymes diffuse to the interstice and go to lymph vessels and capillaries. If protein release is always an indicator of irreversible lesion is still a controversial issue. There is evidence in animal models that high CK activity in plasma does not occur with reversible myocardial damage as that induced by ischemia, but occurs only when the myocardial damage is irreversible, as in infarction. On the other hand, recent, experimental studies suggest that reversible myocardial damage releases small amounts of soluble cytoplasmic proteins (including the soluble troponins). After myocardial lesion, biomarker kinetics depends on different factors: intracellular protein compartment, molecule size, regional lymph and blood flow and the marker's clearance rate. These are the factors that, together with each marker's characteristics, differentiate the diagnostic performance of each one in acute myocardial infarction⁵⁸. In patients who present with suggestive symptoms of non-ST elevation ACS, where the diagnosis of myocardial infarction is not established, the biochemical markers are useful in the confirmation of a diagnosis of infarction. In addition, they supply important prognostic information considering the existence of a direct association between serum marker increase and risk for cardiac events in the short and medium term⁵⁹.

Creatine kinase, its isoenzymes and isoforms

Creatine kinase MB (CK-MB) is the traditionally used marker, although it has diverse known limitations. Ideally, CK-MB should be measured using immunoassay for the determination of its concentration in plasma (CK-MB mass) instead of its activity. This change in measuring standard is partly due to studies which demonstrate a higher sensitivity and specificity for acute myocardial infarction with the use of CK-MB mass⁶⁰. Meta-analyses of retrospective myocardial infarction diagnoses show a 97% sensitivity and 90% specificity⁶¹. CK-MB mass presents as main limitation, increase after damage in other non-cardiac tissues (false-positives), especially after smooth and skeletal muscle lesion. CK-MB isoforms arose as early markers (less than 6 hours) of myocardial lesion. Some studies showed that a CK-MB2/MB1 ratio is more sensitive for myocardial infarction diagnosis on admission and 6 hours afterwards as compared with total CK, CK-MB activity, CK-MB mass and myoglobin^{62,63}. A limitation of CK-MB isoforms is their lower specificity and the technical difficulty in the reproduction of results, justifying their small penetration in the market.

Troponins

Troponins are proteins of the myofibril complex regulation which are not present in smooth muscle. There are three subunits: troponin T, troponin I and troponin C. Troponin C is co-expressed in skeletal muscle fibers of slow contraction and is not considered a specific cardiac marker. In the last decade immunoassay techniques were developed with monoclonal antibodies specific for cardiac troponin C (TnTc) and cardiac troponin I (TnIc). The new assays for cardiac troponins (TnIc and TnTc) have been compared with CK-MB mass in several studies. It is believed that these assays have two main advantages regarding CK-MB: 1) higher specificity for myocardial lesion where CK-MB is found in non-cardiac tissues and 2) ability to detect small amounts of myocardial lesion non detectable by CK-MB assays. Most studies demonstrate that troponins and CK-MB mass have a similar sensitivity for AMI diagnosis in the first 24 hours, always emphasizing a high number of patients with abnormal TnTc and TnIc among patients without infarction. Meta-analyses demonstrated that TnIc has clinical sensitivity and specificity for AMI diagnosis of the order of 90% and 97%, respectively. Taking into account the limitations in establishing a gold standard for the diagnosis of infarction, it is estimated that CK-MB mass and the troponins have a similar performance regarding infarction in the first 12 to 24 hours of evolution. Therefore, cardiac troponins remain high for a longer time after 24 hours of onset of symptoms. TnIc and

TnTc are significantly more sensitive than CK-MB mass. It is estimated that about 30% to 40% of the patients with unstable angina present elevated troponins. Histological evidences to define if this patient group has effectively myocardial necrosis are scarce. There is strong evidence in the international scientific community to believe that individuals with elevated troponins and normal CK-MB mass have "microinfarcts" or some degree of necrosis. Data which help to solve this impasse are the innumerable prospective studies demonstrating that patients without a diagnosis of infarction, but with elevated troponins are at a greater risk of death and other major cardiovascular events in the short or long term, similar to those of patients with non-Q-myocardial infarction^{64,65}. Elevations of these markers are factors indicative of worse prognosis after adjusting for clinical characteristics, electrocardiogram and treadmill test^{59,64,65}. Although troponins are an important prognostic risk factor, they should not be used alone to define the risk of patients with non-ST elevation ACS. Most patients who develop complications present normal troponins. No biochemical marker is sufficiently accurate to determine myocardial damage⁶⁶. On the other hand, abnormal levels of biochemical markers, including troponins, do not mean necessarily a diagnosis of AMI^{64,67}. If clinical presentation of non-ST elevation ACS is not typical, other causes of cardiac lesion related to troponin increase such as heart failure, pulmonary embolism, chronic kidney failure or sepsis should be sought. Troponins also are of value in the evaluation of patients with ischemic alterations on ECG or with clinical signs suggesting anginal pain (Tables 3 and 4). Patients with elevated troponins present increased risk of cardiac events in the first days of hospitalization, apparently with a special benefit regarding invasive management of this population⁶⁸.

Myoglobin

Myoglobin is a very early marker of myocardial necrosis, preceding CK-MB liberation in 2 to 5 hours. Since it is a small molecule it is released in the circulation within 1 hour after myocardial cell death, with peak values being reached in 5 to 12 hours. Myoglobin is not specific for the cardiac muscle and may be released in different conditions which include skeletal muscle damage, muscular dystrophy, kidney failure, severe uremia, shock, trauma and after surgeries. Because it is not a specific cardiac marker, its main advantage seems to be detection of AMI in the first hours of evolution. However, an altered value in the first hours after onset of symptoms does not definitively determine the diagnosis of acute infarction, needing confirmation by other markers. On the other hand, due to high early sensitivity, normal myoglobin may help to rule out the diagnosis

of infarction (high negative predictive value)^{58,69}. Although these markers (CB-MB mass, troponins and myoglobin) are important prognostic factors of cardiac events in the short and long term, they do not need to be measured together in all patients with suspicion of non-ST elevation ACS⁷⁰. Myoglobin is an early marker which may help in some specific situations when the patient is present early in the emergency room (before 4 hours of onset of symptoms) and troponins substitute LDH in the detection of infarction with more than 24 hours to 7 days of evolution.

Note: From the viewpoint of biochemical markers of myocardial necrosis, AMI diagnosis should be established according to the following criteria⁷¹:

1. Troponin T or I: Increase above the 99th percentile in at least one occasion in the first 24 hours of evolution.
2. Maximum value of CK-MB, (preferably CK-MB mass), higher than the upper limit of normality in 2 successive samples; maximum value of CK-MB above twice the maximum limit of normality on one occasion during the first hours after the event. In the absence of CK-MB or troponin, total CK above twice the upper limit may be used, but this biomarker is less satisfactory than CK-MB.

Biochemical markers

Summary of recommendations and evidences

RECOMMENDATIONS CLASS I

- Biochemical myocardial lesion markers should be measured in all patients with suspicion of non-ST elevation ACS. The markers should be measured on admission and repeated at least once, 6-9 hours afterwards (preferentially 9-12 hours after onset of symptoms) in the case the first determination is normal or slightly elevated (*level of evidence: B*).
- CK-MB mass and troponins are the markers of choice (*level of evidence: A*).

Obs: Ideally, troponin and/or CK-MB mass, if available, should be determined in all patients with clinical non-ST elevation ACS suspicion.

RECOMMENDATION CLASS IIA

- Isolated CK-BM activity or associated with total CK may be used if CK-MB mass or troponin are not available (*level of evidence: B*).
- In patients with high-risk factors, as well as in groups of very low risk, troponins may be disregarded (*level of evidence B*).

RECOMMENDATION CLASS IIB

- For patients who arrive early at the emergency room (before 6 hours of onset of symptoms), myoglobin and CK-MB isoforms may be considered in addition to a later marker (CK-MB or troponin) (*level of significance: B*).

RECOMMENDATION CLASS III

- Utilization of lactate dehydrogenase (LDH), aspartate aminotransferase (AST) for the detection of myocardial necrosis in patients with suspicion of non-ST elevation ACS (*level of evidence: A*).

5. Treadmill test

Performing early treadmill test (TT) constitutes a recent concept in the evaluation of patients with non-ST elevation ACS (after stabilization), helping in the prognosis and management of the subsequent therapy. It is considered a safe procedure and should use individualized and adequate protocols for the clinical and biomechanical conditions of the patient, such as the inclination protocol, Naughton or Sheffield (modified Bruce) treadmill tests. They may also be performed using a cyclo-ergometer with progressive attenuated and individualized charges (15W/min). Besides being safe, they contribute to the more precise determination of maximum levels of myocardial oxygen consumption through "double-product" values (maximal SBP x maximal HR) and heat release (VO₂ max) in ml/kg/min or METs which may release myocardial ischemia, that is, the "Ischemic Threshold"^{28,55,72-78}. Electrographic monitoring and records during the test should be performed with the traditional 12 leads. TT positivity is characterized by alterations of the segment-ST, at least in two consecutive leads (depression ≥1.5 mm, or elevation ≥2.0 mm). Presence of precordial pain (angina) and reduction of systolic blood pressure and the chronotropic "deficit"⁷⁹ with progression of exercise reinforce the diagnosis and point to a greater disease severity. Ergospirometry or cardiorespiratory exercise test may be applied to these patients and the results obtained by metabolic, ventilatory and hemodynamic parameters allow to detect the presence of left ventricular dysfunction:

- 1) Oxygen consumption at peak effort (VO₂max) = reduced.
- 2) Oxygen kinetics, evaluated by cyclo-ergometer VO₂/Load (L/min/W) = reduced.
- 3) Oxygen pulse: oxygen consumption/heart beat (ml/beat), related to the systolic volume, in a "plateau" during exercise or reduced at the peak of effort. Preceding angina and/or ST alteration, corresponds to the "ischemic cascade"⁸⁰.

These variables, when present, allow the conclusion that ST alterations observed during the exercise are functionally significant. Studies have demonstrated the following diagnostic accuracy of this test for the presence of coronary artery disease: sensitivity – 73%; specificity – 92%; positive predictive value – 61%; negative predic-

tive value – 95%. A very good diagnostic accuracy is observed to exclude the patients who could have presented symptoms of unstable angina, stabilized, with reduction in hospitalization time.

Importance of the treadmill test in the stratification of patients with chest pain in the hospital emergency room

In the emergency rooms of several hospitals, handling of patients with chest pain became the subject of special attention, taking into consideration that this clinical symptom may express myocardial ischemia, implying eventual complications and risk of death. Usually these patients are transferred to a coronary unit for a two- or three-day observation. However, it was shown that 70% of these patients did not suffer myocardial infarction and many of them present a low risk for coronary artery disease or, even low-risk unstable angina, not needing hospitalization. In 1983, in the St. Agnes Hospital in Baltimore (USA) Dr. Raymond Bahr introduced the first Chest Pain Unit coupled with a laboratory for treadmill tests. Since then, approximately a thousand of such units were created in the US in view of a more efficient, more rapid, safer and less expensive care of patients, mainly those who look for general hospitals. In 1996, the "Hospital Pró-Cardíaco" (Rio de Janeiro, Brazil) started the Chest Pain Project carried out by the staff of the Emergency Unit with the important participation of the Medical Laboratory of the Army which established a daily (including Saturdays, Sundays and holidays), "on call" regimen, up to 10 o'clock p.m. for its physicians specialized in treadmill tests²⁸. TT has been applied mainly to the patients with atypical pain and non diagnostic electrocardiogram after a normal serial enzyme curve. Patients with normal TT are discharged from the hospital. Those who present non conclusive results for coronary artery disease are kept in the hospital. TT is carried out most of the times between 9 and 12 hours after arriving at the emergency room, with the purpose of determining if the patient presents unstable angina⁸¹. Inclination protocol is applied, adapted to the biomechanical conditions of the patient, using the treadmill, with a duration of 10 minutes, with last-generation software, establishing velocity and initial and final inclination, according to assumed maximum heat release, in METs, obtained through the physical ability questionnaire (VSAQ)⁸². Exercise is interrupted by fatigue, electrocardiographic alteration and/or precordial pain. The inclination protocol, with progressive load allowed to more precisely determine the levels of myocardial oxygen consumption (double product) and heat release (METs), promoting myocardial ischemia, that is, the ischemic threshold. Electrocardiographic monitoring and records during the test are performed

with the traditional simultaneous leads. Finally, studies evidenced the inadequate cardiac frequency reduction in the first minute of recovery as predictor of mortality⁸³.

Conclusions

1) The treadmill test is safe and efficient for risk stratification of patients with chest pain who did not suffer clinical complications.

2) Most patients with a pre-test diagnosis of unstable angina, stabilized during stay in the chest pain unit, present a positive treadmill test, that is, with positive clinical ischemic (pain on exercise-induced) or electrocardiographic response (alterations of ventricular repolarization).

3) The treadmill test with an attenuated protocol and adapted to the clinical and biomechanical conditions of the patients presents an excellent diagnostic accuracy for exclusion of those with unstable angina.

4) Negative TT has a high negative predictive value (95%) for coronary artery disease, allowing an earlier and safer discharge from the hospital⁸⁴.

Exercise stress electrocardiogram

Summary of recommendations and evidences

RECOMMENDATIONS CLASS I

- Patients at low-risk (clinical and ECG) and with normal biochemical markers should be referred to treadmill test after 9, ideally after 12, hours, in an ambulatory regimen (*level of evidence B*).
- If performance of the treadmill test is not feasible, or in the case the ECG cannot be interpreted, the patient may be stratified by an ischemia-inducible imaging test (*level of evidence: B*).
- Protocols using treadmill or cyclo-ergometer should be adapted to the clinical and biomechanical conditions of each patient (*level of evidence: B*).

6. Echocardiography

Echocardiography is a complementary method of great use for the evaluation of chest pain on admission to the hospital⁸⁵⁻⁸⁷. It is a non invasive examination and the diagnostic information is available within a short time⁸⁸⁻⁹¹. When the echocardiogram is performed during a precordial pain episode, absence of abnormality in the ventricular segmental contraction is evidence contrary to ischemia as cause of the symptom. Although the echocardiogram is not able to warrant if segmental alteration is recent or pre-recent, the presence of segmental contraction abnormalities reinforces the probability of coronary artery disease, being indicative of infarction, ischemia or both, although it may be also evidenced in cases of myocarditis⁹²⁻⁹⁵. In

addition, not less important etiologies of chest pain, such as aortic dissection, aortic stenosis, hypertrophic cardiomyopathy and pericardiac disease may be evaluated by this method. Important coronary disease is usually found in patients with UA. These patients are in general identified through clinical history and reversible electrocardiographic alteration may be detected, concomitant with pain episodes. When the history and electrocardiogram are not trustworthy, the documentation of abnormality of segmental contraction in the echocardiogram during or immediately after a painful episode in general confirms the diagnosis⁹⁶. Without any risk for the patient, the echocardiogram also evaluates the presence and extension of ventricular dysfunction and, if present, the severity of valvar abnormalities (mitral insufficiency, frequently associated with ischemic etiology). Studies performed in the 1980s already confirmed the usefulness of the echocardiogram in risk stratification of patients with acute chest pain^{92,97}. Sabia et al. studied 185 patients with at least 30-minute acute chest pain or equivalent symptoms of probably cardiovascular etiology. Left ventricular dysfunction was found in one hundred and seven patients. After considering the impact of age, history, physical examination and electrocardiographic abnormalities, the presence of left ventricular dysfunction on echocardiography doubled the available prognostic information⁹⁷. Fleishman et al.⁹⁸ evaluated the capacity of the echocardiogram in the prognostic stratification of 513 patients who were submitted to the examination in the first 30 days after cardiologic emergency care. Ischemic alterations in ECG were present in 48% of the cases. The presence of left ventricular dysfunction (relative risk=3.8) and important mitral insufficiency (relative risk=2.4) were better regarding independent prognostic information when compared to anamnesis, physical examination and ECG data. Mohler et al.⁹⁹ investigated 92 patients with a 60% event rate which is typical for a population of high risk for AMI. Infarction was diagnosed through enzymes and/or ECG. UA was identified in 15 patients by troponin T determination or typical precordial pain of more than 30-minute duration. Based on this criterion, UA may have been diagnosed in excess, leading to a low negative predictive value of the echocardiogram to dismiss the disease. The study's peculiarity is that echocardiograms were only considered positive if the present contractile abnormalities were recent, when compared to evidences in former echocardiograms. Echocardiograms were abnormal in 15 of the 18 patients with AMI and in 12 of the 37 patients with unstable angina. In the UA group, 5 patients presented contractile alterations similar to those in former echocardiograms and were, therefore, considered negative. In the AMI group, 2 patients of

3 who were not detected on echocardiography received thrombolytic therapy. All patients with recent segmental contractility alteration suffered a cardiac event, resulting in a 100% positive predictive value for echocardiography. The negative predictive value was 57%, demonstrating that 43% of the patients with events were not detected by the method. The existing protocols for risk stratification in patients with UA are directed to patients at high risk for adverse cardiac events. They are based on patient evaluation through history, physical examination and electrocardiographic data^{6-8,100-105}. However, such protocols do not observe that adverse event rate is relatively low, even for a high-risk population^{103,106,107}. In addition clinical parameters associated with high risk have low specificity and positive predictive value, that is, many patients classified as being high-risk do not present adverse events^{103,107}. At a time when cost analyses are becoming increasingly important, attention should also be directed to the diagnosis of low-risk patients who may be discharged early from the hospital with consequent decrease of financial costs. This requires definition of diagnostic parameters with high specificity to detect these patients, who are those where a chance of events is very improbable. In this context, the echocardiogram performed on admission to the hospital is more sensitive and specific for the diagnosis of myocardial ischemia^{105,106,108-111}. Stein et al.¹⁰⁹ analyzed 66 patients admitted with a diagnosis of unstable angina who were submitted to echocardiography in the first 24 hours of hospitalization with the following objectives: 1) To identify patients at low risk for adverse intra-hospital cardiac events; 2) To differentiate the low-risk patients from those at high risk. Three echocardiographic predictive factors for adverse events were identified: parietal movement index <0.2, LV ejection fraction <40% and mitral insufficiency degree. One or more echocardiographic predictive factors were present in 32 patients (48%). These predictive factors were specific, presented a high positive predictive value for the identification of high risk and high discrimination power for high- and low-risk patients, regarding the emergence of adverse events (death, AMI, CHF and ventricular tachyarrhythmias) during hospitalization.

Stress echocardiography

Stress echocardiography is gaining increasing acceptance in the evaluation of patients in the emergency room, and early after hospitalization¹¹⁰. Investigation in 26 low-risk patients revealed segmental contraction abnormalities in only 3 patients, none of whom presented a cardiac event¹¹¹. Recently 108 patients were observed for 4 hours with serial enzymes and ECG, being then submitted to a treadmill test or to stress echocardiography with dobuta-

mine. Ten patients presented positive treadmill test. The same happened with 8 patients on stress echocardiography. The tests agreed in 4 patients. All patients with stress echocardiography without evidence of ischemia were free of cardiac events at the end of a 12-month follow-up, as well as 97% of the patients with negative treadmill tests¹¹². Sitges et al.¹¹³ studied 132 patients with a UA diagnosis on stress echocardiography with dobutamine-atropine on the third day of hospitalization. There were no major complications related to the examination. There were no high-risk patients among those of the studied sample. After one year, survival free of events was 91% for those who presented a negative stress echocardiogram, compared to 57% for those who evidenced positive tests ($p < 0.0001$). Left ventricular dysfunction ($p = 0.01$), previous AMI ($p = 0.03$) and positive stress echo were predictors of cardiac events during follow-up.

Concluding, UA diagnosis encompasses a heterogeneous group of patients with different prognosis in the short and long term. Therefore, risk stratification of these patients aiming at rationalization of therapy and decrease of costs related to prolonged hospitalization becomes indispensable. Clinical and electrocardiographic variables are well-defined classifying patients into those at low, intermediate and high risk for death or non fatal AMI in the short term⁶. More recently, incorporation of troponin determination in clinical practice allowed the identification of patients at high risk for complications, implying their safer stratification regarding incidence of events, both during hospitalization and thereafter⁶⁰. Being a feasible, rapid, non invasive and low-cost examination, electrocardiography has the ability to offer additional prognostic information to the above mentioned parameters through evaluation of the global, regional ventricular function and the identification of associated valve disease, and can be used routinely in the investigation of these patients. Stress echocardiography has proven to be a safe method and may be made available for low- and intermediate-risk patients who are clinically compensated for 24/48 h, guiding management to be followed according to the test's result and should not be used in high-risk patients.

Echocardiography

Summary of recommendations and evidences

RECOMMENDATIONS CLASS I

- Transthoracic echocardiogram should be performed in the differential diagnosis with other diseases when there is a clinical suspicion of aorta diseases, pericardium diseases, pulmonary embolism and valvar diseases (*level of evidence: C*).
- In cases of complications subsequent to non-ST eleva-

tion ACS, such as interventricular communication and mitral insufficiency (*level of evidence: C*).

- Stress echocardiography is an alternative to treadmill test in patients who are not able to perform it (*level of evidence: B*).

RECOMMENDATION CLASS IIA

- Patients with current chest pain may be evaluated by echocardiogram at rest in order to determine the ischemic origin or not of the pain (*level of evidence: B*).

7. Nuclear Cardiology: risk stratification in the first 12h after arrival at the hospital Introduction

Nuclear Cardiology plays a definite role in diagnostic, functional and prognostic evaluation of patients with suspicion of or with well-known cardiopathies. Along the last twenty years, especially in those individuals with coronary artery disease, images of myocardial perfusion obtained by Nuclear Medicine techniques have rendered a fundamental contribution to the knowledge and evaluation of ischemic cardiac disease. Additional information through global ventricular function, detection of alteration in segmental contractility and functional reserve of the left ventricular myocardium are clearly established. These integrated data make possible a better management of patients under investigation and/or treatment for cardiopathies in which coronary perfusion and cardiac function may be directly or indirectly affected¹¹⁴⁻¹¹⁶. Regarding non-ST elevation ACS, myocardial perfusion scintigraphy emerges as an important instrument in the estimate of the functional meaning of angiographic coronary stenoses, in the evaluation of the efficacy of therapeutic interventions, and in risk stratification after myocardial infarction. However, the capacity of Nuclear Cardiology to predict the occurrence of acute phenomena (fissure/rupture of the atherosclerotic plaque with thrombosis) is still limited, although becoming the target of new and intense researches¹¹⁷⁻¹²⁰. Several publications demonstrated the diagnostic and prognostic value, as well as the favorable cost-benefit relationship of perfusion scintigraphy in non-ST elevation ACS. Studies of myocardial perfusion are being included in the algorithms for screening and handling of patients in these circumstances. To date, in the US, physicians in emergency rooms make increasing use of Nuclear Cardiology to help in the decision making for patients who are attended with chest pain of undetermined origin, the high sensitivity of the method in the identification of acute myocardial infarction being demonstrated in chest pain centers¹²¹⁻¹²⁵.

Methodology in nuclear cardiology

Nuclear Cardiology may evaluate the heart focusing on aspects of myocardial perfusion, cell integrity, myocardial metabolism, myocardial contractility and global or segmental ventricular function, as evidenced in Chart I. Usually all these evaluations are performed using several tests. Lately, with the incorporation of Nuclear Cardiology resources, last generation equipment (double digital detectors), new radiopharmaceuticals and more sophisticated computer programs, these evaluations may be obtained in a single test only. In Brazil, the most important limiting factors for these methods are the equipments (gamma chambers) and radiotracers (e.g. thallium-201, technetium-99m, isonitrile, tetrophosmin) because they are produced abroad and need to be imported. These problems, involving the cost-benefit issue, restrict the large-scale use of nuclear methods^{26,126-128}. Availability and details of the different methods are summarized in Chart II. In this chart, the techniques under development, or not available, or only available in some centers in Brazil cannot yet be considered routine procedures. Interpretation of test results, qualitative and quantitative analysis, as well as specific protocols, related to the used radiopharmaceuticals are beyond the purpose of this review and are discussed in a specific Guideline on Nuclear Cardiology¹²⁹⁻¹³¹.

Evaluation of the patient with chest pain in the emergency sector

In the US, six millions patients/year are estimated to look for emergency rooms in hospitals because of acute chest pain symptoms. Although approximately 50% of these patients are hospitalized in coronary units for a diagnostic definition, only 10 to 15% of them effectively have an acute myocardial infarction. Among the latter, 2 to 8% are inadequately discharged from the hospital leading to serious medical-legal problems. Several published studies showed that an emergency myocardial scintigraphy at rest considered to be low-risk determines a quite reduced risk of these individuals for subsequent cardiac events. On the other hand, patients with a high-risk scintigraphy have a greatly increased probability to develop acute infarction, to be revascularized (surgery or angioplasty) or to present obstructive coronary lesions on coronariography^{119-121,132}. In the ERASE (Emergency Room Assessment of Sestamibi for evaluation of Chest Pain), where strategies for care of patients with non-ST elevation ACS with normal or not diagnostic ECG were assessed already in the emergency room, 54% admission rate for patients who had a myocardial perfusion scintigraphy and 63% for the others were observed, suggesting that the initial strategy with a scintigraphy at rest is good for risk stratification¹³².

Evaluation of the patient with unstable ischemic myocardial syndrome

Some studies evaluated the use of myocardial perfusion scintigraphy at rest and under stress in patients with unstable angina and after myocardial infarction (with or without ST elevation). Also in this context, individuals with normal images, negative for ischemia or with minor perfu-

Chart I. Parameters of clinical use in nuclear cardiology.

Ventriculography with radionuclides

Parameters (pump function)

- segmental contractility
- left ventricle ejection fraction (LVEF)
- VEF variation (rest/stress)
- final systolic/diastolic volume

Myocardial scintigraphy

Perfusion

Parameters

- extension of perfusion deficit
- number of segments with hypoperfusion
- single or multiple defects
- reversibility of perfusion defects
- fixed defects (fibrosis)
- reversible defects
- radiotracer capture intensity
- transient LV dilatation
- lung radiotracer hyperfixation
- territory of involved coronary artery (e.g. left anterior descending artery)

Metabolism

Parameters (metabolism)

- hyperfixation

Chart II. Methodologies for clinical use in nuclear cardiology

Coronary (flow) and myocardial (metabolism) reserve

Myocardial perfusion scintigraphy

- conventional
- tomographic (SPECT)
 - Thallium-201
 - Technetium-99m isonitrile (MIBI)/tetrophosmin
 - Technetium-99m nitroimidazole
 - Technetium-99m glucarate

Myocardial tomography of metabolism (PET)

- Fluor-16 deoxyglucose

Left ventricle reserve (contractility)

Ventriculography

- equilibrium (synchronized with ECG)
- first passage

Myocardial perfusion scintigraphy (gated SPECT)

- Thallium-201
- Technetium-99m isonitrile (MIBI)/tetrophosmin

sion defects had a better prognosis than the patients with images considered abnormal. The simultaneous information of myocardial perfusion and ventricular function by scintigraphy synchronized with ECG (gated SPECT) is very important, since both the absolute values of left ventricle ejection fraction, as well as the extension of the perfusion defect have a marked predictive value for the occurrence of future cardiac events¹²⁵.

Clinical use of nuclear cardiology in patients with thoracic pain or non-ST elevation ACS

In some medical centers abroad, myocardial perfusion scintigraphy is used to improve the capacity to identify and stratify patient risk in the emergency room with acute pain and, specially, in those with normal or non diagnostic ECG. Injection of the radiopharmaceutical should be performed at rest, while the patient is symptomatic (exceptionally after the end of symptoms), and the images are obtained up to six hours thereafter. These premises lead to the fact that rare Brazilian medical institutions are able to offer them, since availability of radioactive material, technical personnel with training in the method and physicians with experience in image interpretation and valorization is presumed. Myocardial perfusion scintigraphy, with the purpose of defining diagnosis and subsequent management within the first 12 hours after patient arrival at the hospital, should be performed with injection of the radiopharmaceutical at rest and immediate acquisition of images during symptomatic episodes, being indicated in cases of chest pain with normal or unspecific ECG. Myocardial perfusion scintigraphy with administration of radiopharmaceutical during physical stress or pharmacological stimulus in patients with low- or medium- risk non-ST elevation ACS would be after stabilization of the acute symptoms (after 48/72 hours)¹³¹. Stable clinical and hemodynamic conditions are fundamental in both situations. Some of the formerly mentioned limitations also apply to these protocols in Brazil.

Conclusions

The routine search for myocardial ischemia or perfusion alteration by radioisotope imaging methods in patients with typical, atypical or undetermined pain, with or without prior history of coronary artery disease, treated in emergency units is not justified at present regarding clinical or cost/benefit aspects. Clinical information, risk factors for coronary disease, physical examination data, well-established laboratory tests (ECG and biochemical markers), and the possibility of an alternative etiology for the clinical symptoms of thoracic pain should be considered. However, there are literature data which suggest the need for alternative or additional evaluation by Nuclear

Cardiology (myocardial perfusion scintigraphy) in patients in emergency rooms, with acute chest pain and normal or non diagnostic ECG. The probability of occurrence of coronary disease due to presence of risk factors and previous clinical and follow-up data, as well as information regarding myocardial perfusion reserve, should be part of the decision algorithm aiming at additional diagnostic and/or therapeutic orientation. Although there are no sufficient data published so far in the specialized literature, the possibility of simultaneous acquisition of information on perfusion reserve and left ventricle function (LVEF and segmental contractility) by a single examination, myocardial scintigraphy synchronized with ECG (gated SPECT) seems attractive in a scenario where the differential diagnosis of the ischemic origin of chest pain is fundamental. Large scale prospective studies are necessary, with the aim to determine the unique contributions attained with Nuclear Cardiology in the context of evaluation of chest pain or non-ST elevation ACS in the emergency room.

Nuclear cardiology

Summary of recommendations and evidences

RECOMMENDATION CLASS I

- Myocardial perfusion scintigraphy in stress and at rest is an alternative to the treadmill test in patients not able to perform it (*level of evidence: C*).

RECOMMENDATION CLASS IIA

- Patients with chest pain may be evaluated by myocardial perfusion scintigraphy at rest in order to determine the origin, ischemic or not, of the pain (*level of evidence: A*)

Summary of the use of supplementary examinations in AMI without ST elevation and in UA

- ECG: On admission and at least one more within up to 6 hours.
- Biochemical markers: On admission, 6-9 hours, optional at the 4th and 12th hour.
- Treadmill tests: Low-risk patients, after 6 hours of observation and up to 12 hours.
- Echocardiography: To rule out other diagnoses or suspicion of complication.
- Ischemia-provoking imaging test (echocardiography or myocardial scintigraphy): As an alternative to treadmill test.

Criteria for discharge of low-risk patients in the first 12 hours of stratification

- Without pain, clinically stable, a normal ECG or without acute alterations, non elevated biochemical markers and/or negative ischemia-provoking test.

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