

# 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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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 solid meta-analysis of randomized clinical studies.
- **Level B:** Data obtained by less solid 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 2

## Management of intermediate- and high-risk patients

### 1. Hospitalization in and discharge from intensive therapy coronary unit

All patients with intermediate- and high-risk non-ST elevation ACS whenever possible should be hospitalized in an Intensive Therapy Coronary Unit (ITCU). Ideally, the patient should remain in ITCU at least until a definitive management for his/her case is established. In the case the patient is referred to a percutaneous coronary intervention (PCI), he/she should return to ITCU after the procedure. If no complications as for example significant discomfort, hemodynamic instability and/or increase in biochemical markers for myocardial lesion occur, the patient should be discharged the following day. When treatment option is direct surgical myocardial revascularization, the patient ideally should remain in ITCU until the moment of surgery. In the case where clinical drug treatment is indicated, the patient, if stable and not in need for intravenous medication, should be discharged the day after this decision is made.

#### RECOMMENDATION CLASS I

- (level of evidence: *c*).

### 2. Oxygen therapy

In unstable angina hypoxemia may appear during prolonged episodes of myocardial ischemia due to alterations of the ventilation-perfusion ratio, secondary to pulmonary arteriovenous shunt (subsequent to increase in the final diastolic pressure of the left ventricle) and, in addition, formation of pulmonary interstitial and/or alveolar edema. Hypoxemia, in its turn, aggravates myocardial ischemia increasing myocardial lesion.

Restricted and old evidence suggests that oxygen administration is able to limit the extension of acute ischemic lesion<sup>133,134</sup>. Administration of 100% oxygen usually through an intranasal catheter constitutes a routine practice during episodes of prolonged ischemic pain at rest. In cases of severe hypoxemia, monitoring blood oxygen saturation by pulse oximetry or determination of arterial gasometry becomes necessary, with oxygen administration according to the respective results.

Oxygen therapy should be careful in order to not elimi-

nate the hypoxic respiratory stimulus in the presence of chronic obstructive pulmonary disease. Patients with associated pulmonary congestion, cyanosis, proven arterial hypoxemia, or respiratory failure should receive oxygen supplementation and should be accompanied with serial gasometries. Usually oxygen supplementation is maintained for up to four hours after disappearance of pain. In situations where proven persistent hypoxemia exists this will be maintained according to clinical need. Unnecessary oxygen administration for prolonged time may cause systemic vasoconstriction and may be harmful.

#### RECOMMENDATION CLASS I

- Oxygen therapy in intermediate- and high-risk patients (level of evidence: *C*).

### 3. Analgesia and sedation

Precordial pain and the habitually associated anxiety present in non-ST elevation ACS usually lead to hyperactivity of the sympathetic nervous system. This hyperadrenergic state, besides increasing myocardial oxygen consumption, predisposes to the emergence of atrial and ventricular tachyarrhythmias. Thus, the use of potent analgesics is recommended for patients with ischemic pain refractory to antianginal therapy<sup>6</sup>. Morphine sulfate is the analgesic of choice, being administered intravenously at a dose of 1 to 5 mg when pain is not alleviated with the use of sublingual nitrates, or in the cases of pain recurrence in spite of adequate anti-ischemic therapy. If needed, these doses may be repeated at intervals of 5–30 min, monitoring blood pressure. Administration of small increments has the purpose to avoid adverse effects such as hypotension and respiratory depression. Morphine derivatives should be avoided, except in cases of hypersensitivity to morphine when meperidine sulfate in fractionated 20–50 mg IV doses may be used.

The routine use of anxiolytics has been a common practice in Brazil. Often it seems to be dispensable and should be reserved for special situations. A clinical randomized, double-blind study<sup>135</sup> involving 131 male patients with acute myocardial infarction observed that the degree

of anxiety, blood pressure, heart rate and precordial discomfort did not differ between patients treated with diazepam or placebo. Diazepine derivatives have been the most used in this case.

**RECOMMENDATION CLASS I**

- Administration of morphine sulfate in intermediate- and high-risk patients (*level of evidence: C*).
- Administration of benzodiazepines in high-risk patients (*level of evidence: C*).

**RECOMMENDATION CLASS IIA**

- Administration of benzodiazepines in intermediate-risk patients (*level of evidence C*).

#### 4. Nitrates

The use of nitrates is based on their mechanism of action and clinical experience of many years of utilization and where, among other actions, efficacy regarding improvement of the pain symptom is noted. There are no controlled clinical studies which tested the effects of nitrates on clinical outcomes and mortality in unstable angina, although their use is universally accepted. Studies on unstable angina which evaluated them were small and of the observational type<sup>136-138</sup>. Therefore, there is no conclusive information on the benefits provided by this class of medications regarding alleviation of symptoms and reduction in major adverse events (myocardial infarction and death).

The therapeutic benefits of nitrates are related to their effect on the peripheral and coronary circulation. Their vein-dilating effect, decreasing venous return to the heart and the final diastolic volume of the left ventricle reduces oxygen consumption by the myocardium. Additionally vasodilating effects on coronary arteries, normal or atherosclerotic, increase in coronary collateral circulation and inhibition of platelet aggregation are observed. They may be used by oral, sublingual, intravenous and transdermal routes. The sublingual and intravenous routes are the most used for the treatment of acute cases due to their easy adjustment. Small studies which compared the administration routes could not establish significant differences between the sublingual and IV routes<sup>139,140</sup>. Treatment is started in the emergency room administering sublingual nitrate (nitroglycerine, mononitrate or isosorbide dinitrate). In case there is no rapid pain alleviation, these patients may benefit from intravenous administration (nitroglycerine and isosorbide dinitrate are those available in Brazil).

Nitrates are contraindicated in the presence of important arterial hypotension (systolic blood pressure [SBP] <100 mmHg) or previous use of sildenafil in the last 24

h. The sublingual use of nitroglycerine (0.4 mg/tablet) or isosorbide mononitrate (5 mg/tablet) should not exceed 3 tablets, with administrations separated by 5-minute intervals. IV nitroglycerine is used at a 10 µg/min dose with increments of 10 µg every 3 minutes until obtaining symptomatic improvement or reduction in blood pressure (fall in SBP not over 20 mmHg or SBP reaching 110 mmHg), or also increase in heart rate (>10% of the basal HR). The emergence of tolerance to the hemodynamic effects of the drug is expected after 24 hours of use. The tolerance phenomenon has been attributed to depletion of sulfhydryl radicals existing in the arterial wall. These radicals are responsible for the conversion of organic nitrates to nitric oxide. When the oral route is used, tolerance may be reduced by the use of smaller doses and longer intervals between them (minimum of 8 hours); with the intravenous route, instead, periodical increment of the administered doses will be needed. The intravenous treatment should be maintained for 24–48 hours after the last anginal pain and its discontinuation should be gradual.

**RECOMMENDATION CLASS I**

- Use of nitrate in intermediate- and high-risk patients (*level of evidence: C*).

#### 5. Adrenergic betablockers

As in the case of nitrates, controlled clinical experience with the use of betablockers in unstable angina is limited, although greater. Evidence of beneficial effects is based on their mechanism of action, in small controlled clinical studies and on extrapolation of results of studies on stable angina and acute myocardial infarction. Betablockers competitively inhibit the effects of circulating catecholamines. In unstable angina their benefits are related to their action on beta-1 receptors. They decrease heart rate, blood pressure and myocardial contractility, promoting a reduction in oxygen consumption by the myocardium. Despite the inexistence of large-scale randomized studies on evaluation of the action on major clinical outcomes such as mortality, these pharmaceuticals, together with the nitrates are considered agents of first choice in the treatment of non ST-elevation ACS. In unstable angina, only a few and small studies compared betablockers with placebo<sup>141-143</sup>. Although limited studies were not able to detect reduction in mortality, the same does not occur regarding acute myocardial or recent infarction. In this situation the controlled clinical studies were able to demonstrate a significant reduction in mortality. The meta-analysis of five small studies<sup>144</sup> evaluating the use of betablocker therapy in 4,700

patients with unstable angina showed a 13% reduction in the relative risk of progress to acute myocardial infarction. Although developed in patients with AMI with segment-ST elevation, the COMMIT study suggests that routine use of IV betablocker followed by oral use can increase the incidence of cardiogenic shock, mainly when used in the first 24–48 hours of evolution and in patients with clinical signs of left ventricular dysfunction<sup>145</sup>. Thus, the routine use of oral betablocker is recommended in patients without contraindication and its use should be started with the stable patient, in small doses, increasing the doses gradually in order to maintain heart rate around 60 bpm. In the case the patient presents persistent ischemic pain and/or tachycardia (not compensating the signs of cardiac failure), the venous route may be used. Several therapeutic regimens are recommended depending on the selected betablocker. There are no evidences of superiority of one betablocker over the other.

The following chart lists the doses of metoprolol and atenolol, the most used in Brazil.

- **Metoprolol IV:** 5 mg (1–2 min) every 5 min until completing the maximum dose of 15 mg.
- **Metoprolol Oral:** 50–100 mg every 12 h, started 15 min after the last IV administration.
- **Atenolol IV:** 5 mg (1–2 mg) every 5 min until completing the maximum dose of 10 mg.
- **Atenolol Oral:** 25–50 mg every 12 h, beginning 15 min after the last IV administration.

During intravenous administration, heart rate, blood pressure, electrocardiogram and pulmonary auscultation should be carefully monitored.

#### RECOMMENDATION CLASS I

- Oral administration of betablocker in intermediate- and high-risk patients (*level of evidence: B*).

#### RECOMMENDATION CLASS IIB

- IV administration of betablocker in intermediate- and high-risk patients (*level of evidence: B*).

## 6. Calcium channel antagonists

Calcium channel antagonists, although considered a singular group, really constitute a heterogeneous group of drugs which have in common a vasodilating action. This group of drugs with anti-ischemic action decrease calcium flux through the cell membrane, reducing myocardial and vascular contractility, velocity of atrioventricular conduction and sinus node activity. There are three commercially available groups of calcium channel antagonists which are chemically different and have different pharmacologic

effects: the dihydropyridine derivatives (first generation prototype is nifedipine and, as third generation derivative, amlodipine); phenylalkylamines (verapamil) and benzothiazepines (diltiazem). They act by blocking type I calcium channels.

These agents differ regarding their capacity to produce arterial vasodilation, reduce myocardial contractility and delay atrioventricular conduction. The beneficial effects on non-ST elevation ACS are due to a combination of their actions, decreasing myocardial oxygen consumption, afterload, contractility and heart rate besides increasing oxygen supply to the myocardium through the coronary vasodilation they promote. The produced coronary vasodilation is similar and independent of the used agent. Dihydropyridines elicit more peripheral arterial vasodilation and tend to produce reflex tachycardia (more evident with short-acting nifedipine); verapamil and diltiazem tend to cause bradycardia by depressing chronotropism and dromotropism and may lead to atrioventricular blocks (more evident with verapamil). In patients with impaired left ventricular function and/or alterations of the atrioventricular conduction, these drugs should be avoided in general.

To control symptoms<sup>146,147</sup>, calcium antagonists are as efficient as betablockers. However, they do not reduce the incidence of refractory angina, infarction or death; on the contrary, they seem to emphasize the incidence of such complications as suggested by meta-analysis<sup>148</sup>. Up to the present only the first generation agents were evaluated in unstable angina. These deleterious actions were observed with all classes of calcium antagonists<sup>143,144,149</sup> tested for this indication, but there are no conclusive data regarding the more recent dihydropyridines. On the other hand, in cases of myocardial infarction without segment-ST elevation there are evidences that diltiazem and verapamil may have a protecting effect<sup>150,151</sup>. They may be used in the attempt to control refractory ischemic symptoms in patients already in use of nitrates and betablockers at adequate doses, or in patients who do not tolerate the use of these drugs (mainly in cases of contraindication), or also in cases of variant angina. However, the routine use of calcium channel antagonists is not recommended, being contraindicated, particularly, the isolated use of rapid-acting nifedipine.

The standard dose of nifedipine, preferably the extended release preparation, is 10–20 mg three times a day, verapamil 80–120 mg three times a day, diltiazem 60 mg three to four times a day. In unstable angina, diltiazem has been the most used calcium blocker.

#### RECOMMENDATIONS CLASS I

- Intermediate- and high-risk patients. Use non-dihydro-

pyridine derivative in cases of contraindication of beta-blockers (*level of evidence: B*).

- Patients with variant angina (Prinzmetal) (*level of evidence: B*).

#### RECOMMENDATION CLASS IIA

- Extended release dihydropyridines in the presence of refractory ischemia for patients in adequate use of nitrates and betablockers and without ventricular dysfunctions (*level of evidence: B*).

#### RECOMMENDATION CLASS IIB

- Extended release non-dihydropyridine derivatives as substitutes for betablockers and dihydropyridine derivatives with rapidly starting action in patients already in adequate use of betablockers for high-risk patients (*level of evidence: B*).

#### RECOMMENDATION CLASS III

- Dihydropyridine derivatives with rapidly starting action in patients without adequate use of betablockers (*level of evidence: B*).

## 7. Antiplatelet agents

### Acetylsalicylic acid

Coronary thrombosis plays an outstanding role in the release and progression of non-ST elevation ACS symptoms, the use of antithrombotics being essential in the treatment of patients with such syndromes. ASA is the antiplatelet agent of excellence and should be prescribed always except for rare cases of contraindication (allergy or gastric intolerance, active bleeding, hemophilia and active peptic ulcer), or high probability of gastrointestinal or genitourinary bleeding.

ASA blocks thromboxane A<sub>2</sub> (vasoconstricting and prothrombotic substance) formation, interfering in arachidonic acid metabolism and inhibiting formation of cyclooxygenase 1, a fundamental enzyme for the platelet aggregation process.

Analyzing together the data of four controlled clinical studies which assembled more than 2,000 patients with unstable angina treated with ASA, a reduction in the combined outcome death and/or non fatal infarction (control) of 11.8% to 6.9% (ASA) was observed<sup>152-155</sup>.

Gastrointestinal side effects are rare with the use of low doses. Dyspnea and nausea are the most cited. The initial recommended 200 mg dose should be chewed, thus being absorbed by the sublingual route in order to rapidly obtain high ASA blood levels. The recommended oral dose

is 200 mg macerated on arrival of the patient at the hospital, the long-term maintenance dose being 100 mg/day, although doses as low as 75 mg/day are also considered effective<sup>156</sup>. Among all listed medicaments for the treatment of unstable angina, ASA is the one most consistently documented as beneficial, independent of the study design, duration of follow-up and used doses.

#### RECOMMENDATION CLASS I

- Use of ASA in all patients (*level of evidence: A*).

### Thienopyridine derivatives

Ticlopidine and clopidogrel are the commercially available representatives of this class. Both are antagonists of platelet activation mediated by adenosine diphosphate (ADP) which acts on platelet receptor P2Y<sub>12</sub>. They also reduce the circulating fibrinogen level and partially block glycoprotein IIb/IIIa receptors, making difficult their binding to fibrinogen and von Willebrand factor. Initial indication of these drugs was as preferred substitute for ASA in cases of intolerance or allergy. Ticlopidine, less expensive, begins to act between 12 and 14 hours and has a full effect only after some days (which limits its use in the context of non-ST elevation ACS) besides provoking more side effects (fundamentally abdominal pains, nausea, vomiting, neutropenia and/or thrombocytopenia and, rarely, idiopathic thrombocytopenic purpura) as compared to clopidogrel. Ticlopidine was tested in unstable angina in the beginning of the 1990s in a study assembling 652 patients with non-ST elevation MI. A significant reduction of 13.6% to 7.3% ( $p=0.01$ )<sup>157</sup> in the number of deaths and/or non fatal infarction was observed in six months, a reduction very similar to that shown with the use of ASA. In this study which preceded the presently adopted therapeutic recommendations, no ASA and/or heparin were used in the control group.

Regarding clopidogrel, it was tested as compared to ASA, initially in patients with chronic CAD, in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study<sup>158</sup>. In this study, clopidogrel was marginally superior to ASA, showing an 8.7% ( $p=0.043$ ) decrease in relative risk for major events at the end of approximately 2 years of follow-up. In the context of non-ST elevation MI, instead, the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events)<sup>159</sup> study tested the role of clopidogrel in addition to ASA in >12,000 patients with non-ST elevation MI, followed-up for 3 to 12 months (mean of 9 months). At the end of follow-up a 20% decrease in the incidence of events (cardiovascular death, MI and cerebrovascular accident) (OR 0.80; 95% CI 0.72–0.89;

$p=0.00005$ ) was shown in favor of the clopidogrel + ASA group in relation to the ASA + placebo group, at the expense of an increase in the bleeding incidence (OR 1.38,  $p=0.001$ ). Interestingly, the beneficial effects with the use of clopidogrel occurred both in high-risk patients and in those with intermediate or low risk. Subsequent analyses demonstrated that there is an additional benefit with the use of clopidogrel after the first month and until one year after the acute event<sup>160</sup>, that clopidogrel is particularly useful in the subgroup submitted to percutaneous coronary intervention during the hospitalization period<sup>161</sup> and that increase in bleeding with the use of aspirin + clopidogrel fundamentally occurs with higher ASA doses<sup>162</sup>.

The recommended ticlopidine dose is 250 mg twice a day, and of clopidogrel 300 mg as a priming dose and 75 mg/day as maintenance. There are preliminary evidences that for patients being treated with percutaneous coronary intervention (PCI) the clopidogrel priming dose of 500 mg could be more beneficial, but awaits proof of this concept by ongoing studies, fundamentally OASIS-7. Mainly in the case of ticlopidine the follow-up with monthly leukograms during the three first months of treatment is recommended.

When the patients with non-ST elevation MI are treated with PCI, the double block of platelet aggregation (with ASA + a thienopyridine) becomes mandatory based on a study which primarily focused on the PCI context<sup>163</sup>, as also in publications which approach non-ST elevation MI *per se*. The prospectively developed CURE substudy (PCI-CURE) and the CREDO study<sup>164</sup> refer to the latter condition.

The period of thienopyridine prescription after a non-ST elevation MI event is not well defined, but, as mentioned earlier, the CURE study showed benefit up to 12 months (the average time of follow-up in the study was 9 months)<sup>159,160</sup>. If the patient receives PCI with pharmacologic stent, the present recommendation is to maintain the thienopyridine for a period of at least one year after the procedure<sup>165</sup>. The need for discontinuation of the thienopyridine at least five days beforehand in the case the patient will be submitted to surgical routine myocardial revascularization is to be noted due to the risk for severe preoperative bleeding. In conditions of emergency, platelet transfusion should be used.

#### RECOMMENDATIONS CLASS I

- Addition of clopidogrel to ASA in intermediate- and high-risk patients (*level of evidence: A*).
- Addition of ticlopidine to ASA in intermediate- and high-risk patients (*level of evidence: C*).
- Thienopyridines in patients with contraindication for ASA (*level of evidence: B*).

#### Glycoprotein IIb/IIIa receptor antagonists

This class of medicaments blocks the final common route of platelet aggregation, independently of the initial stimulus. Activation of the receptors existing on the platelet surface (about 80,000 for each platelet), called glycoprotein (GP) IIb/IIIa constitutes the final and mandatory mechanism of platelet aggregation consequent to morphologic alteration suffered by the receptor which increases its affinity to bind to a fibrinogen molecule, an element that operates as a binding bridge between two platelets. This process is called platelet aggregation. These same receptors act, by means of fibrinogen binding to von Willebrand factor, on the release of the platelet adhesion process to the endothelial and subendothelial (when exposed) surfaces, a phenomenon previous to platelet aggregation. Antagonists of these receptors block the platelet aggregation process and platelet thrombus formation. These drugs were used in clinical situations with a great potential for platelet activation as, for example, percutaneous coronary interventions, complex or not, and non-ST elevation MI.

Of the compounds of this class, all used IV, only two are commercially available in Brazil (abciximab and tirofiban). Although they belong to the same category, these agents have very different structural, pharmacokinetic and pharmacodynamic properties. Abciximab is a monoclonal antibody which acts as a non competitive and irreversible blocker of GP IIb/IIIa receptors. When administered, it has a short 5–10 min plasma half-life, since the molecule rapidly binds to platelet receptors. Its biological half-life is 6–12 h after an isolated bolus injection. With therapeutic doses an 80–90% block of the surface receptors is attained. Fifty percent of these receptors still continue to be blocked after one week of its use. The recommended dose is a bolus of 0.25 mg/kg, followed by a 0.125 µg administration during 12 hours. On the other hand, tirofiban is a synthetic small-molecule non-peptide derivative that possesses in its molecular structure the RGD (arginine-glycine-aspartate) sequence, recognition site of integrins, present in adhesive proteins of the fibrinogen, von Willebrand factor and vitronectin type, among others. The ability of GP IIb/IIIa to bind adhesive proteins is due to this common sequence. It acts competitively on the GIIa/IIb cell receptor hindering its binding to fibrinogen. The recommended dose is 0.4 µg/kg/min for 30 minutes, followed by the maintenance dose of 0.1 µg/kg/min for 48–96 hours. In the case the use of the drug is started in the hemodynamics room, the initial dose should be 10 µg/kg in a 3-min bolus, followed by 0.15 µg/kg/min during 48–96 hours. Finally, eptifibatide, not commer-

cially available in Brazil, is a synthetic cyclic heptapeptide derived from snake venoms. It belongs to the desintegrin family and has in its molecule the sequence KGD (lysine-glycine-aspartate) which mimics the fibrinogen structure acting as a competitive and reversible GP IIa/IIIb receptor antagonist. Eptifibatid presents rapid dissociation and increased clearance, decreasing bleeding risks. Due to the small size of its molecule it does not cause immunogenicity allowing new administrations if needed. The dose used in the ESPRIT trial<sup>166</sup> (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) in 2,064 patients submitted to elective or emergency stent implantation was 2 µg/kg/min during 18–24 hours after the end of the first bolus. Generically GP IIb/IIIa blockers tend to increase the risk for hemorrhage, and thrombocytopenia is a rare, but not negligible, complication.

In the context of patients with non-ST elevation MI submitted to an essentially “conservative” strategy (no routine performance of early interventional procedures), GP IIb/IIIa blockers had their evidences based on studies in which, besides heparinization, platelet activation was systematically antagonized only by ASA<sup>38,167-171</sup>. Although the results of these studies were quite heterogeneous (in general suggesting a benefit with the use of small-molecule GP IIb/IIIa blockers, but not abciximab), the meta-analysis that included >30,000 patients demonstrated only a 9% reduction in the relative risk for death or infarction at 30 days of follow-up ( $p=0.015$ )<sup>172</sup>, with the benefit restricted to patients at higher risk, fundamentally with elevated troponin and/or with segment-ST depression and/or submitted to PCI (24% at 30 days of follow-up).

Various studies tested the role of GP IIb/IIIa blockade in the context of patients submitted to early interventionist strategy, with performance of PCI whenever feasible<sup>173-180</sup>. The results of these studies are more homogeneous, showing invariably a benefit with the use of these drugs, but at the expense of an increase in bleeding incidence. It should be emphasized that these studies were developed without the routine use of thienopyridines on arrival of the patient at the hospital. Meta-analysis including studies which analyzed the role of GP IIb/IIIa blockers in patients with non ST-elevation ACS with or without ST elevation showed besides significant decreases in death or (re)infarction incidences ( $p<0.0001$ ) also a 21% decrease (RR [risk ratio] 0.79, 95% CI: 0.64–0.97) in the relative death risk at a 6-month follow-up<sup>181</sup>. This meta-analysis also enhanced the concept that when using this class of drugs it is fundamental to be very cautious regarding doses and utilization period of heparins. Thus, a higher bleeding risk was observed

in the GP IIb/IIIa blocker group as compared to the placebo group only when heparin was maintained after PCI but not when its use was restricted to the time of procedure.

The concomitant use of a triple block of platelet aggregation (ASA + a thienopyridine + GP IIb/IIIa blocker) is not sufficiently justified by evidences. The most recent study, ISAR-REACT 2, demonstrated that addition of abciximab to ASA (500 mg) and clopidogrel (600 mg) did not significantly increase the risk for bleeding and was beneficial, but only in the group with increase in troponin levels<sup>180</sup>. On the other hand, the recently published ACUITY-TIMING trial did not show a net clinical benefit (reduction of ischemic/thrombotic complications and hemorrhages) with the strategy of always using GP IIb/IIIa inhibitors (tirofiban or eptifibatid) in comparison with the strategy of their restricted use (only during the intervention)<sup>182</sup>. Patients included in this trial were in use of ASA and clopidogrel initiated up to two hours before the intervention, and the same investigation (in another publication) suggested that the use of a direct antithrombotic substance would be more efficient in the reduction of ischemic complications without increasing the risk for hemorrhages<sup>183</sup>.

Regarding data of the “real world”, two studies which were developed based on the same US databank (National Registry of Myocardial Infarction 4), analyzed the issue in patients with AMI without ST elevation. The first, published in 2003, demonstrated a significant decrease in mortality of patients submitted or not to a GP IIb/IIIa blocker: it should be emphasized that the adjusted models did not take into account the concomitant use of thienopyridines<sup>184</sup>. The second, more recent, compared the isolated use of a GP IIb/IIIa blocker (65% of the population), clopidogrel (16.1% of the population) or the combination of both (18.8% of the population), the comparison between the groups being additionally stratified regarding performance or not of intervention. When the results of the outcome, consisting of death, non fatal reinfarction and severe bleeding were corrected by propensity scores, the treatment with GP IIb/IIIa blockers did not show benefit in the group treated with intervention, being inferior in the group of conservatively treated patients.

### Glycoprotein IIb/IIIa receptor antagonists

#### Summary of recommendation and evidences

Early interventional strategy

#### RECOMMENDATION CLASS I

- High-risk patients. Use of abciximab and tirofiban when opting for not administrating thienopyridines (*level of evidence: A*).

**RECOMMENDATION CLASS IIB**

- High-risk patients. Use of abciximab in addition to ASA and thienopyridines (*level of evidence: B*).

Conservative strategy

**RECOMMENDATION CLASS IIA**

- High-risk patients. Use of tirofiban when opting for not administering a thienopyridine (*level of evidence: B*).

**RECOMMENDATION CLASS IIB**

- High-risk patients. Use of tirofiban in addition to AAS and thienopyridines (*level of evidence: B*).

**RECOMMENDATIONS CLASS III**

- Routine use of abciximab in high-risk patients (*level of evidence: B*).
- Use of abciximab or tirofiban in intermediate-risk patients (*level of evidence: B*).

Obs: abciximab should be used as close as possible to the beginning of the procedure.

## 8. Inhibitors of the renin-angiotensin system

These are potent drugs used in the treatment of arterial hypertension, cardiac failure and in some groups of patients with coronary artery disease. They are successfully used in cardiac failure, arterial hypertension, diabetes mellitus, left ventricular dysfunction after acute myocardial infarction and even in recent acute infarction without manifestations of cardiac failure. There is no evidence of benefits of their early use but some studies suggest that they may be useful in the chronic phase after the acute episode. The HOPE (The Heart Outcomes Prevention Evaluation) study<sup>186</sup> demonstrated that patients at high risk for cardiovascular events, frequently with important atherosclerotic arterial disease, (in general compromising the coronary territory) and independently of the phase in which they were, benefited from the use of 10 mg/day ramipril in the long term. In a 5-year follow-up, reduction in the relative death risk of 26% ( $p < 0.001$ ), of 20% in infarction ( $p < 0.002$ ) and of 32% in stroke ( $p < 0.001$ ) was observed. Similar results were also shown in patients with chronic coronary disease using perindopril<sup>187</sup>. On the other hand, the PEACE trial which tested trandolapril did not show benefits in the general population (it is assumed that it was a very low-risk population) in spite of the observation of less incidence of events with the use of trandolapril in the subpopulation with  $< 60$  mg/mL/min/ $1.73\text{m}^2$  estimated glomerular filtration<sup>188,189</sup>. Although not being routinely

used in unstable angina, renin-angiotensin system inhibitors have their indication recognized for the control of systemic arterial hypertension and left ventricular dysfunction.

**RECOMMENDATION CLASS I**

- Administration of ACE inhibitors in intermediate- and high-risk patients with left ventricular dysfunction, hypertension or diabetes mellitus (*level of evidence: A*).
- Administration of angiotensin II receptor blockers in intermediate- and high-risk patients with contraindication of ACE inhibitors (*level of evidence: C*).

**RECOMMENDATION CLASS IIA**

- Administration of ACE inhibitors in all intermediate- and high-risk patients (*level of evidence B*).

## 9. Antithrombin agents

Although some disagreement existed in the past<sup>190</sup>, to date predominates the concept that erosion (fissure) or atherosclerotic plaque rupture are essential mechanisms which release the pathophysiologic events which clinically exteriorize as UA and AMI with or without segment-ST elevation, respectively<sup>191-193</sup>. With a more or less extensive atherosclerotic plaque fissure, blood constituents as well as coagulation factors are exposed to the contact with subendothelial material. This leads to platelet activation, adhesion and aggregation, and to accelerated thrombin generation as essential mechanisms for subsequent thrombosis localized at the fissure site. These two mechanisms (involving platelets and thrombin) act synergistically, with mutual potentiation for the maintenance and amplification of the thrombotic process. Among other effects, thrombin is a potent platelet activator, as is factor Xa of the coagulation cascade; in addition, activation of the thrombin cascade by factors Va and Xa occurs at the platelet membrane. Besides these pathophysiologic disorders which occur at the sites of vascular lesion causing the clinical event, there is convincing evidence that in patients with non-ST elevation ACS a transient prothrombotic state with systemic characteristics is present<sup>194,195</sup>.

Finally, it should be considered that increment in thrombin activation in patients with non-ST elevation ACS has a negative prognostic connotation<sup>196,197</sup>. For these reasons, the use of a standard antithrombotic drug (non fractionated heparin – NFH) concomitant with antiplatelet therapy for the routine treatment of patients with the various non-ST elevation ACS modalities is quite justified. Although, through an indirect mechanism, the main anticoagulant effect of heparin depends on its specific binding to anti-

thrombin which occurs by action of a pentasaccharide sequence present in approximately one third of heparin molecules. The heparin-antithrombin complex is altered from the stereotaxic viewpoint, allowing simultaneous coupling to both thrombin and factor Xa, which are thus neutralized. The conformational alteration of the heparin-antithrombin complex molecule is only possible when heparin contains a minimum of 18 polysaccharide units, corresponding to approximately 6000 daltons. Meta-analysis of 6 randomized studies performed until 1996 approves the virtually generalized management during the last century of treating patients with non-ST elevation MI with the combination of ASA and NFH<sup>198</sup>. In these studies the most used heparinization regimen was the conventional one, with an initial 5000 IU injection followed by 1000 IU/h infusion and adjustment of APTT to double the control value. Although it is theoretically recommendable to adjust doses according to the patient's weight in order to allow a more effective anticoagulation in terms of the desired APTT<sup>199</sup>, there is no demonstration of clinical advantages with this therapeutic regimen. The intermittent NFH injections, instead, showed to be effective in only one report of the literature, but not in the RISC study nor in another smaller earlier trial<sup>200</sup>. A quite generalized routine is that of adjusting the heparinization regimen for APTT values between 1.5–2.0 times the laboratory control (50 to 70 s) according the strategy of the TIMI-III trial<sup>1</sup>.

During the investigation to better understand the structure of conventional heparin (NFH) it was observed that its polysaccharide chains may be depolymerized by several physical and chemical processes so as to obtain also heterogenous compounds, but of lower molecular weight which received the generic name of fractionated or low molecular weight heparins (LMWH)<sup>201,202</sup>. By definition, a LMWH should have an average molecular weight below 8000 daltons and with at least 60% of its molecules complying with this criterion<sup>203</sup>. Typically compounds with a molecular weight between 2000 and 10000 daltons are obtained from 5000- to 30000-dalton NFH. LMWH have as common characteristic, although to a variable degree, the ability to preferentially bind to factor Xa (and less to factor II) inactivating it. This characteristic gives them the singular capacity to bring about an antithrombotic effect without substantially altering (if not used at high doses) the usually utilized coagulation tests to monitor the therapeutic effect of NFH.

Another marked difference derives from the fact that LMWH do not bind to plasma proteins nor to cell surfaces (platelets, macrophages and osteoblasts) and to the en-

dothelium as intensely as NFH. Thus, LMWH when administered subcutaneously presents a higher bioavailability and half-life compared to NFH.

Three LMWH are available for clinical use in Brazil, all tested in international, multicenter studies, prospectively designed to compare their clinical efficiency to that of NFH in the treatment of patients with non-ST elevation ACS: nadroparin, dalteparin and enoxaparin.

The FRAXIS trial demonstrated that nadroparin is similar to NFH and that there is no additional gain with the longer use of the product beyond the hospitalization phase<sup>204</sup>.

Three studies tested dalteparin in the context of non-ST elevation ACS and demonstrated that this compound is better than placebo and similar to NFH, in addition to corroborate the previous finding of lack of usefulness of this drug's use for a longer time<sup>205-209</sup>.

In the same period two studies were published comparing enoxaparin with NFH, in terms of clinical efficacy and safety in the treatment of patients with UA and AMI without ST elevation. Summarizing, they demonstrated for the first time that a LMWH (in this case enoxaparin) was superior to NFH, besides corroborating those mentioned before, realizing that there is no additional benefit with the use of the drug after the hospitalization phase. Perhaps more important, the joint analysis of the two studies demonstrated a significant decrease in the incidence of "hard" events, death or (re)infarction, in favor of enoxaparin compared to NFH, the benefits being maintained for at least 1 year after the initial treatment<sup>210-215</sup>.

In conclusion, the formerly mentioned studies demonstrated that fraxiparin and nadroparin are similar to NFH, enoxaparin being superior to this compound. However, these studies were developed in a relatively low-risk population, not necessarily submitted to aggressive antiplatelet therapies or to early invasive stratification. For this reason several studies were developed with the objective to evaluate if with contemporaneous non-ST elevation MI treatment the formerly demonstrated benefits would be maintained.

The mentioned initial relatively small studies, fundamentally tested the role of enoxaparin as compared to NFH in populations treated with GP IIb/IIIa blockers and submitted to early invasive stratification. In general, they were in favor of LMWH, except for the A to Z study, which showed similarity among the heparins<sup>216-218</sup>. Because of the need for a definitive response on the matter, the SYNERGY trial was developed including 10,027 high-risk patients (at least 2 of the following markers of high risk: age >60 years, elevated biochemical necrosis markers, ST depression or transient elevation), submitted to intensive clin-

ical treatment and early invasive strategy. In the enoxaparin and NFH groups the use of GP IIb/IIIa blockers occurred in 56% and 58% of the cases, respectively. Coronary angiography was performed in 92% of the global population, on average 21 hours after arrival at the hospital, PCI was performed in 46%, and 47% and myocardial revascularization surgery in 19% and 18%, respectively. From the viewpoint of efficacy, the main study outcome was death or (re)AMI at 30 days, with an incidence of 14% and 14.5% in the enoxaparin and NFH groups, respectively ( $p=0.396$ ). There also were no significant differences regarding each of the parameters alone, but all analyses reached the goals of non-inferiority. Also, when analyzing specifically the population submitted to PCI, it was shown that enoxaparin was as efficient as NFH regarding the different analyzed parameters which included unsuccessful procedure, acute occlusion or need for emergency myocardial revascularization surgery. From the viewpoint of important bleeding, there was a significantly higher incidence in the enoxaparin group when considering the TIMI criterion (9.1% vs 7.6%,  $p=0.008$ ), but not when considering the GUSTO criterion (2.9% vs 2.4%,  $p=0.106$ ), or blood transfusion (17% vs 16%,  $p=0.155$ ). Incidence of cerebral hemorrhage was  $<0.1\%$  in both groups. Approximately 1/3 of the analyzed population used both tested heparins during the hospitalization period; this was allowed according to protocol in specific situations, and in approximately 800 cases this occurred due to crossover (therefore, the investigator's fault). Specifically analyzing the population with "consistent" therapy (using only one of the tested heparins –  $n=6,138$ ), the authors demonstrated benefit in favor of enoxaparin (death or AMI incidence at 30 days 12.8% vs 15.6%, respectively,  $p=0.0029$ ). Finally, analyzing the patients who suffered or not "crossover", increase in bleeding incidence was found without there being any benefit in terms of effectiveness. However it is important to emphasize that these analyses were "post-hoc" which in a certain way limits their conclusions. More recently, Mahaffey et al.<sup>219</sup> published the 6-month (death/AMI) and 1-year (death) follow-ups of the analyzed population, fundamentally demonstrating that the initial results were maintained during the follow-up period. Petersen et al.<sup>220</sup>, analyzing together 6 randomized studies which compared enoxaparin with NFH ( $n=21,946$  patients), found significant decreases in death/AMI incidences at 30 days, in favor of LMWH, with odds ratios of 0.91 (95% CI 0.83–0.99) in the global population (NNT – number needed to treat=107) and 0.81 (95% CI 0.71–0.94) in the population with "consistent" therapy (NNT=72). There were no sig-

nificant differences regarding important bleeding or blood transfusions between the groups. In order to minimize the bleeding problem, enoxaparin should have its maintenance dose decreased by 25% (0.75 mg/kg, 12/12 hours instead of 1.0 mg/kg 12/12 hours) in the elderly, and in patients with creatinine clearance  $<30$  (1.0 mg once a day).

These clinical differences regarding the various LMWH have been explained by differences between them related to the different manufacture processes which ultimately explain different profiles related to their different molecular weights, absorption and elimination times, platelet activation and action on factors such as von Willebrand<sup>202,221-226</sup>.

Thus it may be concluded that LMWH in general are as efficient as NFH<sup>227,228</sup>. However, enoxaparin apparently is superior to NFH<sup>220</sup>. In the patients who received enoxaparin for the treatment of non-ST elevation MI and are referred to PCI in up to 8 to 12 hours after the last SC dose, there is no need for additional anticoagulation. In those who undergo PCI between 8 and 12 hours, an additional 0.3 mg/kg IV dose should be administered immediately before the procedure<sup>217</sup>. Finally, it is suggested to maintain the initially used heparin during the whole heparinization period, avoiding the concomitant or alternate use of LMWH and NFH.

### Antithrombin agents

#### Summary of recommendations and evidences

##### RECOMMENDATION CLASS I

- Use of non fractioned heparin in all patients (*level of evidence: A*).
- Use of low molecular weight heparin in all patients (*level of evidence: A*).

##### RECOMMENDATION CLASS IIA

- Use of enoxaparin in preference to NFH except when myocardial revascularization surgery is planned for the next 24 hours (*level of evidence: A*).
- Alternate or concomitant use of NFH or LMWH should not be performed (*level of evidence: B*).

It is important to remember that in the high-risk patient submitted to GP IIb/IIIa blockers and early invasive stratification preference should be given to NFH or enoxaparin, since these are heparins with specific studies in this situation.

Two other compounds, hirudine and bivalirudin, not yet available in Brazil, have direct antithrombotic properties, potentially useful in patients with heparin-induced thrombocytopenia. Combining the results of the OASIS-2 study<sup>229</sup> with those obtained by TIMI-9B and GUSTO IIb,

22% reduction in RR (relative risk) of death/AMI after 72 hours ( $p=0.0004$ ), 16% after one week ( $p=0.002$ ) and 10% after 35 days ( $p=0.016$ ) were shown. These evidences together are compatible with the notion that hirudin, a direct antithrombotic, could represent a more efficient alternative than NFH to treat patients with non-ST elevation ACS, maintaining a reasonable safety profile. However, there are no operational advantages of its use, requiring monitoring of the anticoagulant effect and intravenous administration. It is possible also that its advantages of a direct combination, as compared to NFH, are partially counterbalanced by at least theoretically plausible limitations: "exhaustion" of availability, since binding to thrombin is irreversible, and insufficiency of doses to antagonize the platelet activation induced by thrombin in the concentrations provided by the clinical use (in its turn limited by the risk of hemorrhagic complications). Thus probably the attenuation of the initially observed benefit in the mentioned studies could be explained. A systematic revision of the results of studies which tested bivalirudin in patients with all types of non-ST elevation ACS (including the patients of what would be the TIMI-8 study) included a total of 5,674 patients<sup>230</sup>. Of these, 4,603 were related to elective percutaneous revascularization procedures and other 1,071 presented several types of non-ST elevation ACS. Meta-analytic methods were used to compare the results of 4 comparative randomized studies on bivalirudin with NFH in 4,973 patients, observing that the first was associated with a significant reduction ( $p=0.02$ ) in the odds ratio of death or AMI (OR=0.73, [95% CI=0.57–0.95]) at 30–50 days of follow-up. With bivalirudin also occurred a significant reduction in the odds ratio of severe hemorrhage as compared to NFH (OR=0.41 [95% CI=0.32–0.52],  $p<0.001$ )<sup>230</sup>. Therefore, the authors considered that bivalirudin would constitute an antithrombotic agent of at least an efficacy comparable to NFH but with a better safety profile for clinical use in patients with non-ST elevation ACS. However it is necessary to consider that the studies included in the meta-analysis were quite heterogeneous and that the results were most probably influenced by the great number (87%) of patients which were treated with percutaneous coronary angioplasty reported in the HAS study (Hirolog Angioplasty Study). Some of the above mentioned limitations pointed out for hirudine also apply to this other direct antithrombotic, as regards easiness of use and absence of cost-efficacy/benefit studies. Thus, hirudine and bivalirudine will be used in intermediate- or high-risk patients in the place of heparins when induced thrombocytopenia syndrome occurred. More re-

cently, the ACUITY trial showed that in patients with non-ST elevation ACS bivalirudin is similar to the association heparin + GP IIb/IIIa blocker regarding ischemic events (7.8% and 7.3%, respectively), but with a lower incidence of bleeding. On the other hand, it seems to be as efficient as heparins (NFH or LMWH) when used together with GP IIb/IIIa blocker (7.7% and 7.3%, respectively, for ischemic events) with the same safety profile regarding important bleeding (5.7% and 5.3%, respectively)<sup>183</sup>.

Another product, not yet available in Brazil, is the fondaparinux, tested in the OASIS-5 trial against enoxaparin. In this study, the primary death/AMI/refractory ischemia outcome at 9 days of evolution was similar in the enoxaparin and fondaparinux groups (5.8% and 5.9%, respectively), with also similar incidences of each of the outcome components. However, bleeding incidence, including major bleeding, was unfavorable regarding LMWH (4.0% vs 2.1%, respectively,  $p<0.0001$ ). Interestingly, death incidence at 30 days of evolution was higher in the enoxaparin group (3.5% vs 2.9%,  $p<0.03$ )<sup>231</sup>.

## 10. Diagnosis and risk stratification with supplementary methods

In patients with non-ST elevation ACS, risk stratification should be a continuous process, since the initial clinical evaluation, passing through supplementary tests already discussed in these Guidelines, and culminating with the additional methods presented as follows. These methods to be used during the first hospitalization days may basically be divided into two categories:

a) Intravascular hemodynamic tests with performance of coronary angiography, radiologic contrast ventriculography, and measurement of intracardiac pressures. Essentially this allows direct visualization of the coronary lumen, with evaluation of the extension and severity of the obstruction and analysis of the diastolic and systolic ventricular function, global (ejection fraction) and regional<sup>232</sup>.

b) Non invasive tests, as treadmill test, echocardiogram and nuclear tests.

Contrary to the intravascular test which provides anatomic information about the coronary circulation, the non invasive methods evaluate the occurrence of myocardial ischemia. Thus, the approach is functional, and the presence or absence of coronary injury is indirectly evaluated by the corresponding occurrence or not of ischemia. These methods provide also indirect (treadmill test) or direct (echocardiography and nuclear tests) support regarding ventricular function.

Both categories of methods are used for diagnostic and prognostic complementation, in order to better define medical management of patients at intermediate or high risk for complications.

Since some years an intense controversy is observed regarding the relative merits of two fundamental cardiologic strategies based on the respective initial and preferential use of each of these two test categories to evaluate patients with these clinical characteristics<sup>233</sup>. According to the so-called early "interventionist" strategy, the intermediate-/high-risk patients are routinely approached as soon as possible using the intravascular method<sup>1</sup>. This strategy has the aim to complement the prognostic stratification and the identification of the most appropriate form of treatment (clinical, percutaneous or surgical revascularization) through the angiographically disclosed coronary anatomy and the combined study of the ventricular function. A direct corollary of this management is the frequent possibility of percutaneous or surgical myocardial revascularization, if possible and indicated, on the basis of coronary angiographic anatomic results.

Early interventionist strategy allows to immediately identify:

a) The approximately 10-20% of patients without lesions or with hemodynamically non significant coronary obstructions (<50%) and who may be discharged early from the hospital with an excellent prognosis once they adequately control their risk factors;

b) The 5–10% of patients with significant lesion of the left coronary and the 20–30% of patients with multiarterial involvement (with or without ventricular global dysfunction), who usually benefit from myocardial revascularization.

Through the non invasive strategy, also characterized in some contexts as "conservative" and, more recently, called "selective interventionist" intermediate- or high-risk patients are stabilized with clinical treatment and submitted early to non intravascular functional tests. Only if there are clinical indications of persistent or recurrent ischemia, or if abnormal results appear on non invasive tests, the patients are referred to coronary angiography.

The interventionist and non invasive strategies were compared in several observational records and in 11 randomized studies. The records attest that there is a great variability of management concerning these two modalities of approach in patients with non-ST elevation MI in the several participant countries, the result generally being inconclusive regarding the best strategy to be adopted<sup>30,234-236</sup>.

Of the 11 controlled and randomized studies, four

were small<sup>237-240</sup>. The remaining 7 included substantially higher numbers of patients (>900) and were developed since the end of the 1990s up to the present. From the methodological viewpoint, a wide variation of inclusion and exclusion criteria, of time between the beginning of symptoms and coronary angiography performance, and in the subsequent revascularization intervention, in concomitant therapies and even in the interpretation of results is noted. As a consequence the obtained results are quite heterogeneous and, eventually, discrepant regarding several relevant issues<sup>1,209,241-245</sup>.

Although there is no unanimity regarding the best strategy, the notion that most of the more recent evidences support the "interventionist" strategy should be recognized. This view is supported by three independent meta-analysis studies, using varied statistical techniques with the homogeneous conclusion of the superiority of the "interventionist" strategy in regard to decrease in incidence of death and non fatal (re)infarction<sup>246-248</sup>. It should be marked that the benefit of the "interventionist" strategy tends to intensify after the initial phase in which, paradoxically, the risk of the use of this strategy can be greater, as suggested by long-term follow-up of patients included in some of formerly mentioned studies<sup>249,250</sup> and also in a recent meta-analysis<sup>251</sup>.

It is important to emphasize that the sum of evidences demonstrates that the benefit of the "interventionist" strategy is greater the greater the risk of the patient. In addition, an adequate antithrombotic regimen with antiplatelet and antithrombotic drugs is fundamental for the success of this approach. Finally, since none of the studies comparing "interventionist" or "conservative" strategies used pharmacologic stents or more efficient antithrombotic regimens, there is a wide improvement potential for both here discussed strategies.

### **Hemodynamic and coronary angiographic study Summary of recommendation and levels of evidence**

#### **RECOMMENDATION CLASS I**

- Performance of hemodynamic and radiologic contrast coronary angiographic study in intermediate- and high-risk patients (*level of evidence: A*).

#### **RECOMMENDATION CLASS III**

- Routine coronary angiography should not be indicated – even for patients with intermediate/high risk, in the following situations: patients with important comorbidity or reduced life expectancy (for example, respiratory, renal, hepatic failure, and cancer with an established

prognosis); and patients who *a priori* refuse myocardial revascularization (*level of evidence: C*).

**Observation 1** – Class I recommendations for coronary angiography are specially emphasized when hemodynamic and/or electric instability, refractoriness to optimized drug treatment and recurrence of spontaneous or provoked (non invasive stress tests) myocardial ischemia, detected subjectively or objectively occur.

**Observation 2** – As pointed out above, there is no consensus about the most appropriate time to conduct the intravascular study, there being managements from immediate indication to those which generically advocate a period of hospitalization. The ISAR-COOL study which prospectively analyzed the problem suggests that there is no advantage in waiting too long since conducting the study in the first 6 hours from randomization (on average 2.4 hours) was more efficient than its performance after 72 hours (average, 86 hours)<sup>244</sup>.

**Non invasive tests for ischemia diagnosis and prognostic evaluation**

**a) Treadmill test (TT)**

The electrocardiographic TT may constitute the essential approach in patients with non-ST elevation ACS when other non invasive resources are not available and if there is no indication for the intravascular strategy. Besides offering diagnostic support, it has a recognized prognostic value; positive tests are associated with a higher incidence

of coronary events in one year, when compared to negative tests. It is a cheap, safe method of easy application in men and women after an acute episode. Its negative predictive value is very high, from 98% to 100%, although with a modest positive predictive value of approximately 50%, positive treadmill test being infrequent in the population indicated for this procedure<sup>252-254</sup>. The usefulness of this strategy is confirmed due to its safety and efficiency in reducing the period of prolonged hospitalizations. The test should not be carried out in patients with persistent ST-T and T alterations.

**CLINICAL STUDIES AND RISK CLASSIFICATION BASED ON RESPONSES TO THE TREADMILL TEST (TT)**

The prognostic values of TT after a non-ST elevation ACS episode has convincingly been demonstrated. Several authors developed prognostic scores after analysis of the responses to TT obtained in thousands of patients<sup>255</sup>. Most consider that an early positive test (ST depression equal to or >1 mm in the first stages of the Bruce protocol identifies a population with a high risk to develop cardiovascular events<sup>256</sup>. Using the CASS registry Weiner et al.<sup>257</sup> analyzed 4,083 patients identifying 12% as being high-risk, based on segment-ST depression >1 mm and inability to complete the 1<sup>st</sup> stage of the Bruce protocol. Annual mortality in this group was over 95%, while patients who completed the 3<sup>rd</sup> stage without segment-ST depression (considered low-risk) presented a less than 1% annual mortality.

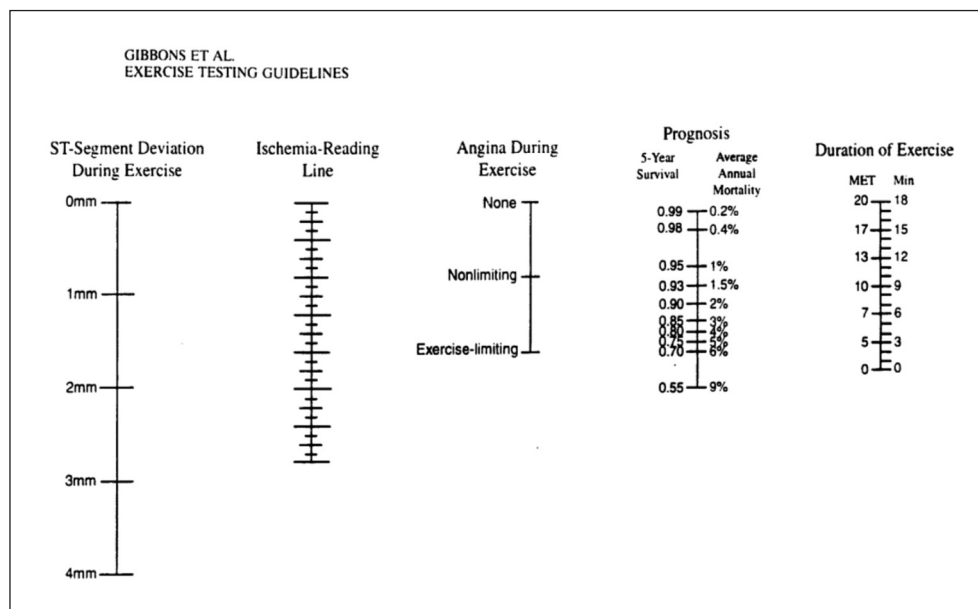


Figure. Duke risk score.

In the RISC study<sup>258,259</sup> 740 men with UA and non-Q AMI were examined. The main mortality predictors were the number of leads with ST depression and time of exercise. Segment-ST depression in 3 leads and low tolerance to effort correspond to a 2.5-fold risk increase for future events (infarction, class II or IV angina and death). On the other hand, presence of anginal pain during the test did not add prognostic information related to infarction and death except when accompanied by ST depression. But it was an independent predictor for the development of class II or IV angina. This study demonstrated also that medication did not influence the test result after acute CAD. In the FRISC study<sup>260</sup> the low tolerance to effort, arterial hypotension and ST depression in 3 leads were significantly associated with a higher risk for death and infarction in 5 months of evolution. In this study 29% of the high-risk patients had events, contrary to only 5% of the patients considered low-risk. For Butman et al.<sup>261</sup> patients with positive tests (ST depression equal to or >1 mm) presented much higher incidences of complications (AHA class III and IV angina, revascularization surgery, infarction or cardiac death) than patients with negative tests (58% × 29%) after 1 year of evolution, with 73% sensitivity, 85% specificity, 87% positive and 71% negative predictive values.

#### RISK CLASSIFICATION

Parameters measured by the test determine the residual ischemia degree and are useful for cardiac performance evaluation. Residual ischemia is estimated by ST-segment behavior and presence of anginal pain. Cardiac performance is evaluated by time of exercise, behavior of blood pressure and the double product. Cardiac performance has presented a better correlation with mortality as compared to other parameters.

In practice the Duke score proposed by Mark et al.<sup>262</sup>, converted to a nomogram to facilitate its clinical use may be utilized (Figure). With this score the prognosis is determined by segment-ST deviation, presence of anginal pain on effort and time of exercise or equivalent in METs.

By intersection of the lines the 5-year survival prognosis is obtained, classifying the patients into 3 different groups:

- a) high risk: annual mortality over 4%
- b) intermediate risk: annual mortality between 2% and 3%
- c) low risk: annual mortality equal to or below 1%

The main independent predictors of survival free of events (death and AMI) in 1 year, in a multivariate regression analysis were the number of leads with segment-ST

depression and the reached maximum load. In 766 patients with non segment-ST elevation ACS in the FISC study and who had TT before discharge and troponin, the ST depression and troponin T combination identified patients in groups with AMI or death risk ranging from 1% to 20%. In 395 women of the FRISC 1 study, with stabilized non ST-elevation ACS who were submitted to symptom-limited TT, the risk of cardiac events ranged from 1% to 19%<sup>252</sup>.

#### SAFETY

It is assumed that TT in stabilized patients is a safe method with a 0.5% incidence of complications (death or AMI) in up to 24 hours after the test<sup>252,263,264</sup>.

#### INTERMEDIATE RISK

With the purpose to estimate the prognosis and help the clinical decision in intermediate-risk patients, TT is indicated in this group of patients 24 to 48 hours after complete clinical stabilization (hemodynamic stabilization, absence of either clinical or electrocardiographic active ischemia, absence of new Q-waves, absence of clinical cardiac failure signs, normal serologic enzymes) once there is capacity to perform the test.

**Exclusion criteria** – Infarction, persistent segment-ST or T-wave alterations, enzyme increases, age over 75 years, digitalis use, presence of ventricular preexcitation, basal ST-segment depression >1 mm, pacemaker rhythm, left bundle branch block, peripheral arterial disease, marked left ventricular hypertrophy, peripheral arterial disease, chronic obstructive pulmonary disease, anemia, hemorrhages, thromboembolic accidents, aortic aneurism, signs of heart failure and other conditions imposing obstacles to performance of the exercise.

**General recommendations and protocol** – The tests should be performed on a treadmill or ergometric bicycle, in a hospital environment, and always limited by symptoms. For the treadmill the modified Bruce protocol may be used (2 stages of 1.7 mph with 0% and 5% inclination, preceding the standard Bruce protocol), or a protocol that is not staged, and is individualized and adapted to the clinical and biomechanical conditions of the patients (ramp-type protocol). For the bicycle, start should be with 10 to 30 watts, with 10 watts/minute increments.

#### CRITERIA FOR TEST INTERRUPTION

- a) Chest pain.
- b) Important dyspnea, fatigue or dizziness.
- c) Substantial exhaustion (Borg scale 17/20).

d) Segment-ST depression  $>2$  mm measured at 0.08 seconds from the J point.

e) Segment-ST elevation.

f) BP fall ( $>15$  mmHg) or 10 mmHg fall with a 1-minute interval

g) Severe arrhythmia (supraventricular or ventricular tachycardia, ventricular 5-beat bigeminy, polyfocal ventricular extrasystoles and 2<sup>nd</sup> and 3<sup>rd</sup> degree AV blocks.

#### PROGNOSTIC MARKERS

##### 1. Electrocardiographic

a) Maximum segment-ST depression.

b) Segment-ST elevation.

c) Number of leads with Segment-ST depression.

d) Duration of segment-ST depression.

e) Time of beginning of segment-ST alterations.

f) Presence of effort-induced arrhythmia (ventricular tachycardia, ventricular bigeminal extrasystoles in more than 5 complexes, 2<sup>nd</sup> and 3<sup>rd</sup> degree atrioventricular blocks.

##### 2. Hemodynamic

a) Attained maximum HR.

b) Attained maximum double product.

##### 3. Clinical

a) Angina.

b) Low tolerance to effort (less than 5 METs).

#### Treadmill test

##### Summary of recommendations and evidences

###### RECOMMENDATION CLASS I

- Performance of treadmill test in intermediate-risk patients (*level of evidence: B*).

###### RECOMMENDATION CLASS IIB

- Performance of treadmill test in high-risk patients after 48 h (*level of evidence: C*).

###### RECOMMENDATION CLASS III

- Performance of treadmill test in high-risk patients before 48 hours (*level of evidence: C*).

Therefore, TT as early strategy ( $<48$  h) is formally contraindicated in high-risk patients. However, TT performed after 48 hours of complete stabilization of clinical signs already during hospitalization may be indicated in patients submitted to coronary angiography when functional evaluation of a known lesion or determination of risk before discharge from hospital is necessary. The test should be performed in a hospital environment by personnel with experience in the method.

#### b) Echocardiographic tests

Transthoracic echocardiography, of low cost and easy

execution at the bedside, is the test of choice in hospitalized patients with intermediate or high risk according to the non invasive strategy for global ventricular function and regional contractility evaluation, deriving very important and early prognostic elements<sup>87,109,265-269</sup>.

###### RECOMMENDATION CLASS I

- (*level of evidence: B*)

In special circumstances needs to be substituted for or complemented by transesophageal examination, for example, when transthoracic test evaluation is impossible<sup>270</sup>.

###### RECOMMENDATION CLASS IIA

- (*level of evidence: B*).

###### STRESS ECHOCARDIOGRAPHY

Stress echocardiographic test allows the observation of transient regional contraction abnormalities, indicative of induced ischemia. Pharmacologic stress by dobutamine administration is safe and efficient in this context and also promotes prognostic information. However, the same restrictions of caution and contraindications exposed for TT apply to this method. The following are considered responses indicative of higher risk: incapacity of increasing ejection fraction or its  $>5\%$  decrease on effort and regional contraction defects during stress. Responses of segmental contraction improvement in dyssynergic areas with initial dobutamine doses (5 to 10  $\mu\text{g}/\text{kg}/\text{min}$ ) identify myocardial feasibility in these areas "stunned" by prior ischemia<sup>271-275</sup>.

###### RECOMMENDATION CLASS I

- Stress echocardiography in patients in whom doubts persist after being submitted to TT (*level of evidence: B*).

###### RECOMMENDATION CLASS IIA

- Stress echocardiography as alternative to the Treadmill Test (*level of evidence: B*).

###### RECOMMENDATION CLASS III

- Stress echocardiography in high-risk patients (*level of evidence: C*).

###### STUDIES WITH MYOCARDIAL PERFUSION EVALUATION

Echocardiographic contrast agents are solutions containing gas microbubbles the size of an erythrocyte whose interface with the liquid medium is highly refringent, improving the echocardiographic signal of the medium containing them. The presently used microbubbles are formed basically of perfluorocarbons and present sufficient stability, when injected by the peripheral endovenous route, to cross the pulmonary barrier and contrast the left cardiac cavities and the coronary circulation. The echographic contrast makes a better definition of endocardial borders possible allow-

ing a more adequate evaluation of the parietal myocardial thickening and of the global and segmental contractile function of the left ventricle, at rest and under stress. In addition, contrast agents allow a more accurate measurement of ventricular volumes and ejection fraction, mainly in cases of suboptimal images and have a proven usefulness in the definition of alterations of the anatomy<sup>271,276,277</sup>.

Although microbubbles improve the definition of endocardial borders, their greatest contribution to stress echocardiography is their potential to allow the detection of myocardial perfusion alterations. The development of contrasts containing microbubbles of a smaller diameter and greater stability associated with technological advances, such as the intermittent harmonic image and the image with a low mechanical index, allowed the study of myocardial perfusion by echocardiography.

The stress echocardiographic test with microbubbles allows the observation of regional transient perfusion abnormalities, indicative of induced ischemia. Pharmacologic stress with dobutamine administration is safe and efficient in this context, and also provides prognostic information. Extensive regional perfusion defects during stress are indicative of severe CAD. Responses of segmental contraction improvement in dyssynergic areas with initial dobutamine doses (5 to 10 µg/kg/min) identify myocardial viability in these regions "stunned" by prior ischemia.

Image with real-time perfusion is a new technique which uses low ultrasound energy with reduction in microbubble destruction. The use of echocardiographic contrasts during dobutamine stress echocardiography with real-time image analysis allows a simultaneous evaluation of myocardial perfusion and segmental motility alterations.

Contrast echocardiogram in intermediate-risk patients with non-ST elevation ACS is extremely useful for bedside AMI diagnosis. Myocardial microcirculation can be evaluated with this method since microbubbles are microvascular markers which behave like erythrocytes and, therefore, do not reach areas of microvascular obstruction. In this way areas with infarction do not present this contrast and are easily detected on echocardiography<sup>271,278-280</sup>.

**RECOMMENDATION CLASS IIA**

- Transthoracic contrast echocardiography for Doppler signal improvement in patients with suboptimal image or transthoracic contrast echocardiography for delineation of endocardial borders during stress echocardiography in patients with suboptimal images at rest (*level of evidence: B*).

**RECOMMENDATION CLASS IIB**

- Stress echocardiogram with microbubbles in interme-

diated-risk patients in whom doubts persist after treadmill test performance (*level of evidence: B*).

**RECOMMENDATION CLASS III**

- Stress echocardiogram with microbubbles in high-risk patients (*level of evidence: C*).

**c) Nuclear Medicine methods**

Myocardial perfusion scintigraphy (MPS) and nuclear ventriculography have a great diagnostic and prognostic value in acute and chronic CAD<sup>281-283</sup>. MPS is basically indicated in cases the treadmill test is impossible to be performed and in patients in whom there are difficulties of adequate stress electrogram interpretation: presence of significant segment-ST unlevelling during respiratory maneuvers and postural alterations; left ventricular overload; bundle branch block; presence of extensive electrically inactive areas; use of drugs which alter ventricular repolarization or make electrographic interpretation difficult (digitalis, betablockers, antiarrhythmics, antidepressives); cardiac and non cardiac diseases associated with basal electrocardiographic alterations. One of the main indications of MPS is the possibility of its early application to non-ST elevation ACS with a wide safety margin, using vasodilating agents such as dipyridamole and adenosine. When performed in the presence of anginal pain in the emergency room, even without administration of "stressing" agents to induce ischemia, regional heterogeneity of the flow provoked by obstructive CAD can be observed<sup>284,285</sup>. Regarding other tests, MCP showed to be superior in this application. The possibility of synchronizing scintillographic tomographic study (gated SPECT) with ECG should also be emphasized to evaluate regional systolic function and measure ventricular ejection fraction with a single test. There is a clear demonstration of effectivity and clinical safety of MPS when used in clinically stabilized patients after the initial event, according to studies utilizing planar or tomographic techniques, thallium-201 or Tc-99m-sestamibi, and dynamic physical effort or pharmacologic stress<sup>286-291</sup>. The various studies are consistent regarding the demonstration that patients with a UA diagnosis showing a normal scintigraphy during stress belong to the subgroup with a markedly reduced risk for severe events, approximately 1% in one year, while detection of reversible defects expresses a very unfavorable prognosis with an event rate of the order of 20% for the same time of follow-up. Finally, there is unequivocal demonstration in the literature and the experience of many centers that MPS methods mainly based on thallium-201 (but also, in many circumstances, with Tc-99m-marked compounds) are very valuable for the detection of myo-

cardial viability in ventricular dyssynergic regions. This may occur in conditions of a stunned myocardium, after acute ischemia and consequent arterial recanalization, or of myocardial hibernation in the presence of chronic ischemia.

### Myocardial perfusion scintigraphy

#### Summary of recommendations and evidences

##### RECOMMENDATION CLASS I

- In intermediate-risk patients in whom doubts persist after TT performance, or in those without possibility to be submitted to TT (*level of evidence: B*).
- For identification of presence/extension of ischemia in patients who cannot be catheterized, or when its results are not sufficient for the establishment of management (*level of evidence: B*).
- After catheterization, for identification of the artery related to the event (region to be revascularized), and/or risk stratification (*level of evidence: A*).
- In patients with dissynergic ventricular regions in whom proving or excluding the presence of viable myocardium is needed in order to direct the therapeutic management (*level of evidence: A*).

##### RECOMMENDATION CLASS IIB

- As first option (*level of evidence: B*).

##### RECOMMENDATION CLASS III

- In high-risk patients before the first 48 hours of patient stabilization (*level of evidence: C*).

### Nuclear angiocardigraphy

#### Summary of recommendations and evidences

##### RECOMMENDATION CLASS I

- In intermediate- and high-risk patients for identification of right ventricle involvement (*level of evidence: A*).

##### RECOMMENDATION CLASS IIA

- In intermediate- and high-risk patients for identification of right ventricle involvement (*level of evidence: C*).

## 11. Myocardial revascularization

### A) Surgical

Myocardial revascularization controls persistent ischemia and avoids progression to acute myocardial infarction. It alleviates symptoms, prevents ischemic complications and improves functional capacity and prognosis. It may be performed both through surgical and percutaneous coronary intervention. Its indications have varied according to the different currents of opinion, since those

where extremely conservative positions are taken to those which predict its indiscriminate use. Regional variations from 0.2% to 36% are observed regarding its indication<sup>30</sup>. Concerning intervention modalities, in the past indications for surgery predominated. However, development of angioplasty, mainly with the use of stents, led to predominance of percutaneous interventions always when they could be performed. Even so, the number of patients who benefit from early surgical revascularization remains high.

Indications for surgical revascularization in unstable angina are similar to those adopted for patients with stable angina. The use of surgical revascularization should take into account the coronary anatomy (degree of obstruction, location of lesion and importance of vessel) and left ventricular function. Life expectancy, associated diseases, severity of symptoms and amount of viable myocardium at risk also influence decision making.

### Myocardial revascularization surgery

#### Summary of recommendation and evidences

##### Intermediate-risk patients

##### RECOMMENDATIONS CLASS I

- Left coronary artery trunk lesion (*level of evidence: A*).
- Triarterial disease with decreased left ventricular function (ejection fraction <0.50) (*level of evidence: A*).
- Biarterial lesion with proximal impairment of the left anterior descending artery and decreased left ventricular function (ejection fraction <0.50) or presence of provoked ischemia (*level of evidence: A*).
- Uni- or biarterial lesion, without proximal impairment of the left anterior descending artery, with high-risk criteria in non invasive test and extensive area of myocardium at risk (may receive alternative treatment with percutaneous coronary intervention) (*level of evidence: A*).

##### RECOMMENDATIONS CLASS IIA

- Uni- or biarterial lesion without impairment of the left anterior descending artery, but with moderate area of viable musculature and ischemia on non invasive test (may receive alternative treatment with percutaneous coronary intervention) (*level of evidence: B*).
- Unilateral lesion with important proximal impairment of the left anterior descending artery (may receive alternative treatment with percutaneous coronary intervention) (*level of evidence: B*).
- Multiarterial disease in diabetics (*level of evidence: B*).
- Reoperation for patients with multiple stenoses in grafts, particularly when there is impairment of flow to the left anterior descending artery (*level of evidence: C*).

**RECOMMENDATION CLASS III**

- Non significant coronary stenoses (<50%) (*level of evidence: C*).

**High-risk patients****RECOMMENDATIONS CLASS I**

- Left coronary artery trunk lesion (*level of evidence: A*).
- Triarterial disease with decreased left ventricular function (ejection fraction <0.50) (*level of evidence: A*).
- Biarterial lesion with proximal impairment of the left anterior descending artery and decreased left ventricular function (ejection fraction <0.50) or when there is presence of ischemia provoked in a previous test, or if performed to evaluate stunned myocardium (*level of evidence A*).
- Uni- or bilateral lesion, without proximal impairment of the left anterior descending artery, with high-risk criteria in non invasive test and extensive myocardial area at risk (may receive alternative treatment with percutaneous coronary intervention) (*level of evidence: A*).

**RECOMMENDATIONS CLASS IIA**

- Uni- or bilateral lesion without proximal impairment of the left anterior descending artery, but with a moderate area of viable musculature and ischemia in non invasive tests (may receive alternative treatment with percutaneous coronary intervention (*level of evidence: B*)).
- Uniarterial lesion with important proximal impairment of the left anterior descending artery (may receive alternative treatment with percutaneous coronary intervention) (*level of evidence: B*).
- Multiarterial disease (*level of evidence: B*).
- Reoperation for patients with multiple stenoses in grafts, particularly when there is impairment of flow to the left anterior descending artery (*level of evidence: C*).

**RECOMMENDATION CLASS III**

- Non significant coronary stenoses (<50%) (*level of evidence: C*).

**B) Percutaneous coronary intervention**

There is to date a continuous and intense increase in the number of indications for Percutaneous Coronary Intervention (PCI) in the context. Among several factors this is due to the fact that this procedure became more efficient and safe with stent implant and coadjuvant use of the GP IIb/IIIa blocker complex<sup>173-176,178</sup> and ADP blockers (see Antiplatelet Agents), thus amplifying the series of indications for percutaneous coronary intervention. Thus, multiarterial patients, those with severe ventricular dysfunction and anatomically more complex lesions are approached more safely. Ideally, the procedure should be performed at

least 24 h after disappearance of the clinical symptoms. Success, major complications and severe ischemic event indices after PCI are favorably affected by the initial stabilization. Contrariwise, the results are negatively affected by the refractoriness to clinical treatment. Other aspects which influence indication for PCI in the context are:

- 1) Extension of coronary disease (uni-, bi- or triarterial).
- 2) Number of lesions to be approached.
- 4) Morphologic lesion characteristics.
- 5) Technical difficulty of the procedure.
- 6) Amount of myocardium at risk.
- 7) Patient's clinical condition.
- 8) Associated diseases.

In addition it should be mainly considered that as far as the choice between this method and that of surgical revascularization is concerned, circumstantial factors regarding the experience of each center may be decisive for the results to be obtained. This method of myocardial revascularization has the following recommendations:

**RECOMMENDATIONS CLASS I**

- Patients with uni- or biarterial lesions, with significant proximal lesion in the left anterior descending artery, and with a great area of the myocardium at risk and ischemia by functional tests (*level of evidence: B*).
- Patients with multiarterial lesions, favorable coronary anatomy, normal left ventricular function and without diabetes mellitus (*level of evidence: B*).

**RECOMMENDATIONS CLASS IIA**

- Uni- or biarterial patients, but without proximal involvement of the left anterior descending artery, but with moderate area of the myocardium at risk and ischemia on functional tests (*level of evidence: C*).
- Patients with focal lesions or multiple stenoses in aortocoronary saphenous vein grafts, and who are high-risk candidates for surgical reoperation (*level of evidence: B*).

**RECOMMENDATION CLASS IIB**

- Patients with tri- or biarterial lesions, proximal lesion of the left anterior descending artery, depressed left ventricular function (EF <50%) or diabetes mellitus, but with anatomy in favor of percutaneous approach (*level of evidence: B*).

**RECOMMENDATIONS CLASS III**

- Patients with hemodynamically insignificant coronary stenoses (reduction of lumen diameter less than 50%) (*level of evidence: C*).
- Patients with significant lesion in left coronary trunk who are candidates for surgery (*level of evidence: C*).
- Uni- or biarterial patients without significant proximal

lesion in the left anterior descending artery or with symptoms atypical for myocardial ischemia, or who did not receive an adequate clinical therapy, or in whom no ischemia was demonstrated by functional tests (*level of evidence: C*).

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