CARDIOLOGY

Risk Stratification in the Patient with Non ST Segment Elevation Acute Coronary Syndrome

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Patients hospitalized with unstable angina (UA) or with a non-ST segment elevation myocardial infarct (NSTEMI) are at increased risk of suffering refractory angina, recurrent myocardial infarct (MI), and death. These patients need to be evaluated more aggressively. According to the last published guidelines (2002) of UA/NSTEMI by the ACC/AHA Task Force, these patients should be categorized in a risk scale as: low, intermediate or high. This should be done in the initial evaluation, which includes: medical history, physical exam, an electrocardiogram (ECG) and cardiac markers. The TIMI risk score should also be used as complementary in this risk assessment.

High risk patients, without contraindications, should be managed more aggressively with coronary angiography. On the other end, low risk patients, and some intermediate, may be evaluated more conservatively with early non-invasive studies for further assessment of ischemia and prognosis.

Key words: Unstable angina, Non-ST segment elevation myocardial infarct, Risk stratification, Coronary angiography, Stress testing, Cardiac markers

Heart disease remains the leading cause of death in the United States (US) with about 700,000 cases reported in 2002, mainly related to coronary artery disease (CAD) (1).

Approximately 8 million patients present yearly to the emergency departments (ED) with chest pain complaints in the United States (2). Of these, five million are initially judged to have a suspected ACS and are admitted to the hospital. Less than half of these patients are ultimately discharged with a final diagnosis of a true coronary process. This would seem to suggest a more passive and conservative (overprotective) approach in the care of patients presenting with non-traumatic chest pain. The cost for these negative cardiac evaluations has been estimated to be $6 billion in the US each year. On the other hand, close to 1% of the patients (40,000) initially evaluated and discharged from the ED with an apparent non-cardiac chest pain will ultimately have an acute MI. This of course not only has a negative consequence to the patient, but it can also results in possible malpractice liability. Both extremes are negative and reflect the remaining unsolved challenges still present for the diagnosis of ACS and for the implementation and adherence of better risk stratification tools and strategies.

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ACS mostly results from a destabilization of a coronary plaque, which eventually leads to platelet activation, aggregation and thrombus formation. The end result will depend according to the severity and the balance between this thrombotic process and the opposing fibrinolytic endogenous response. This presentation may be viewed as a spectrum of severity from its most benign presentation of unstable angina, from a sub-occlusive stenosis, to its most severe consequence of sudden cardiac death (SCD) mostly related to an occlusive thrombus.

Clinical spectrum of ACS:

1. **Unstable Angina (UA)**
2. **Non-ST segment elevation MI (NSTEMI)**
3. **ST segment elevation MI (STEMI)**
4. **Sudden Cardiac Death**

It is important to recognize that this patient is at constant risk of evolving along this spectrum, such as, from UA to STEMI, and should be monitored closely during the initial 24-48 hrs. Immediate determination of an acute STEMI or new LBBB in the setting of a clinical ACS is critical for early reperfusion therapy, either with primary percutaneous coronary intervention (PCI) or fibrinolytic therapy, different to the patient with UA or NSTEMI.

Fundamentally, this terminology has evolved along clinical lines based upon this divergence in therapeutic approach to STEMI versus NSTE-ACS (UA and NSTEMI) based on the presenting ECG. Unstable angina and NSTEMI are considered to be closely related conditions, sharing a common pathogenesis and clinical presentation

but differing in severity. Both are principally mediated by the formation of an arterial "white" thrombus, composed of platelets and fibrin. This thrombotic lesion may progress to a partial or subtotal obstruction of the artery, reducing distal coronary flow and leading to myocardial ischemia. NSTEMI may result from a sustained ischemia for more than 20-30 minutes, or from thromboembolic events down stream resulting in occlusion of distal vascular bed and myocardial necrosis. NSTEMI is then confirmed by the elevation of cardiac biomarkers of necrosis. On the other hand, UA is favored in the presence of a similar clinical picture but in absence of biomarker elevation.

UA is defined as angina pectoris or equivalent symptoms with at least one of the following three characteristics:

1) Resting chest pain (or at minimal effort) more frequent or sustained, usually lasting more than 20 min.
2) New onset of exertion angina in the preceding 2 months, of at least Class 3 of the Canadian Cardiovascular Society Classification (CCSC, see table1).
3) Acceleration of preexisting angina in the preceding two months, to at least a CCSC III.

The natural history of an evolving NSTE-ACS consists of a stabilization of the coronary plaque with restoration of the blood flow and a regression of this lesion into a chronic more stable plaque, versus a negative evolution with the potential to worsen within the above described spectrum to STEMI or death. These adverse events usually occur within the first 4-6 weeks of the presenting event. The reported 30-day risk of death is between 2-7%. In the GUSTO II-b (3) the 30-day mortality was higher in the NSTEMI group compared to the UA group, 5.7% vs. 2.4% respectively ($p<0.001$). This difference was also sustained after one year with 11.1% vs. 7% respectively ($p<0.001$). Also, the incidence of a new infarction or re-infarction after 30-days was higher in the NSTEMI group compared with the UA group, 7.5% vs. 4.8% respectively ($p<0.001$).

Table 1. Angina Classification according to the Canadian Cardiovascular Society

Class	Activity that provokes angina	Activity Limitation
I	Prolonged exertion	None
II	Walking > 2 blocks	Mild
III	Walking < 2 blocks (ordinary activity)	Moderate
IV	Minimal effort or at rest	Severe

Risk Analysis

Risk analysis should begin immediately upon arrival of the patient to the ED, to decide further therapy and care. This consists of assessing the likelihood of CAD and the risk of suffering an adverse cardiac outcome. The last includes death, new or recurrent MI, recurrent UA, or refractory angina that requires hospitalization and/or urgent coronary revascularization. According to the last published guidelines (2002) of UA/NSTEMI by the AHA/ACC Task Force (4), these patients should be categorized in a risk scale as: low, intermediate or high (Table 2).

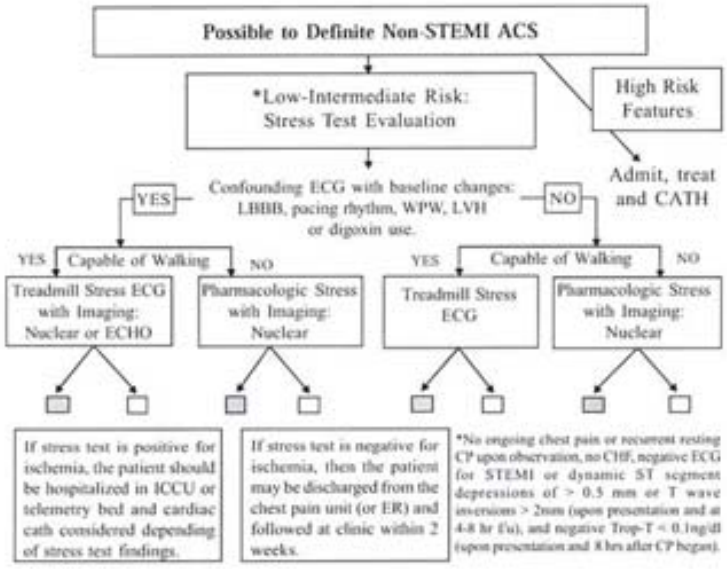
Table 2. Short-Term Risk of Death or Nonfatal Myocardial Infarction in patients with UA/NSTEMI

Features	High	Intermediate	Low
	At least one	Without high risk characteristics & one of the following:	Without high or intermediate risk characteristics & the following:
History	Worsening symptoms, less than 48 hours from presentation.	Prior MI, CABG, PCI, PVD or cerebrovascular disease	
Character of pain	Prolonged chest pain of > 20 minutes and at rest.Age > 75.	Prolonged chest pain (>20min) at rest, but resolved. Angina (<20min) that resolved with NTG or rest.	Angina that increased in frequency, severity, or duration. Lower threshold, but not at rest.
Clinical findings	Angina with CHF findings: S3, rales, hypotension or new MR	No CHF	No CHF
ECG	Transitory changes of ST > .05mV, new LBBB or VTach	T wave inversions >0.2mV, or old MI (Q waves)	Normal without ST segment changes.
Cardiac markers	Marked cTn elevation	Mild cTn elevation (not diagnostic of MI)	Normal

UA= instable angina, NSTEMI=Non ST segment elevation myocardial infarct MR= mitral regurgitation, LBBB= left bundle branch block, VT= ventricular tachycardia, CHF=congestive heart failure cTn=cardiac troponin
*Risk of adverse cardiac event (unstable angina, no fatal MI, urgent coronary revascularization, and death)
Adapted from the ACC/AHA guidelines for UA/NSTEMI, 2002.

This initial risk assessment will determine how aggressive will the therapy be regarding the use of glycoprotein IIb-IIIa inhibitors, closer intensive care monitoring and early invasive coronary angiography versus a more conservative care with a non-invasive evaluation of ischemia. The majority of patients with an intermediate risk may be admitted to the telemetry ward, while the patient of high risk should be hospitalized to an intensive care unit. On the other hand, the low risk patient, with a normal or non-diagnostic initial ECG and with negative cardiac markers, should remain in observation for at least 8-12 hours. During this period, if the patients clinical condition does not deteriorate and his subsequent ECG and cardiac markers remain negative, then the patient may be evaluated early with a regular treadmill stress test or a pharmacologic stress test for the diagnosis of ischemia and risk stratification (Figure 1). Stress testing patients categorized as low risk has been reported to be safe (5-7). The patients with a negative stress test may be discharged from the ED with a close follow-up in outpatient clinics. The negative predictive value for adverse cardiac events with this test is high. Amsterdam and his colleagues (5) found that only one patient out of a total of 582 with negative stress tests suffered from a non fatal MI, versus 16 (adverse events) out of 114 patients with positive stress tests for ischemia. The patients with positive stress test for ischemia should remain hospitalized for a more thorough evaluation, including coronary angiography if favored.

Figure 1. Non-invasive Evaluation of the Patient with Unstable Angina with Low to Intermediate Short-Term Risk



Cardiac catheterization is the diagnostic test of choice for CAD. However this test is invasive and has potential risks for the patient, besides added costs that should be properly weighed before using indiscriminately. It has been reported that upon evaluating patients with admission diagnosis of UA with coronary angiography, 10% to 20% have normal coronary arteries or insignificant CAD. Meanwhile, about 20-25% have three-vessel CAD and between 5-10% have left main (LM) stenosis. For this reason, coronary angiography should be considered in high risk patients (and in some intermediate risk) to determine the severity of CAD and possible benefit from further percutaneous or surgical coronary intervention. The patients considered low to intermediate risk (Figure 1) should be evaluated non-invasively with either an exercise stress test or a pharmacologic stress with complementary cardiac images to further supplement on this risk analysis. There are multiple non-invasive tests available that vary on there predictive value, availability and costs. The optimal study will also depend on each patient. The most important determinants for test selection include: the pre-test probability of having CAD, the baseline ECG and the patient's capacity for walking on the treadmill. The predictive value of these tests and how to select between them will be discussed ahead.

Clinical Characteristics

A good tool for risk stratifying the patient (with UA) according to the medical history is the Braunwald classification (see Table 3). This classification separates the patient according to three criteria: 1) severity of symptoms, 2) clinical circumstance and 3) treatment intensity. Severity is graded from I to III, according to presence of resting angina and evolution of symptoms. Class III corresponds to resting angina of less than 48 hours of evolution. Meanwhile angina post-MI, CCS ≥ 3 of less than 2 weeks from the event, is the clinical circumstance of highest risk. This last was observed in the TIMI III registry of patients presenting with non-STEMI ACS, where the risk of non-fatal MI or death in 42 days was higher in patients with angina post-MI, followed by resting angina, compared to those with non-resting angina; 18.4%, 4.2% and 1.4% of events respectively (6-8). Other independent predictors included age, male sex, hypertension, and the use of maximal anti-angina medical therapy (8). Refractory angina has also been associated

Table 3. Braunwald Classification of Unstable Angina

Severity of symptoms:	
Class 1	: New-onset, severe, or accelerated angina. Not at rest.
Class 2	: Resting angina. Not in the preceding 48hrs (subacute).
Class 3	: Resting angina in the preceding 48 hrs.
Clinical Circumstances:	
Class A	Secondary unstable angina- extrinsic condition with fixed stable CAD (ex. anemia, fever, hypoxemia, hypotension, tachycardia, etc.)
Class B	Primary unstable angina
Class C	Post-infarction UA (within 2 wks)
Treatment intensity:	
1. Absence of treatment or minimal.	
2. Occurring in presence of standard therapy (x3).	
3. Occurring despite maximally tolerated doses of triple therapy.	

with a worse prognosis. This was observed in a sub-analysis by Armstrong (9) from the GUSTO II-b, with a 25.4% of MI in patients with refractory angina, compared to 9.2% in patients with non-refractory angina and 2.6% in the group without angina recurrence. The one year mortality was also significantly higher with 20% versus 9.5% in those without refractory angina. Other patients that have proved to be at a higher risk from suffering further adverse cardiac events include: diabetes mellitus, peripheral vascular disease, and heart failure (Killip >2) (10-13).

Electrocardiogram

In UA the ECG may present with ST segment depressions, transient ST segment elevations and/or T wave inversions in 30-50% of the cases, depending on the severity of the clinical presentation (14-15). Pop and his colleagues reported that 15% of the patients with acute MI and 25% of those with UA have non-diagnostic ECGs (16). Its utility increases if it is done while the patient has ongoing chest pain. This presenting ECG also has a short and long term prognostic value. Analysis of the GUSTO II-b revealed that the patients with ACS had different mortality rates (at 6 months) according to the ECG findings: 3.3% in those with only T wave inversions, 6.7% in those with ST segment elevations (treated with fibrinolytics) and 8.8% in those with ST segment depressions (15). Even though the patients with ST segment elevations had a higher early mortality this was surpassed by ST segment depressions on the longer run. Further findings from the TIMI III Registry have included LBBB and ST segment depressions of ≥ 0.05 mV as independent predictors for the development of death or MI at one year, 22% in those with LBBB and 11% in those with ST segment depression ($p<0.001$) (14). The risk related to ST segment depression increases according to the magnitude of depression (17, 18).

An ECG substudy form the FRISC II, revealed that the presence of ST segment depression was also related angiographically to worse CAD (three-vessel CAD and LM stenosis), found in 45% in those with ST segment depression compared to 22% in those without (19). T wave depressions are sensitive for ischemia assessment, but are less specific, unless they are pronounced (≥ 0.3mV).

Cardiac Markers

The most sensitive and specific cardiac markers for the detection of MI are the cardiac troponins: either cardiac troponin T (cTnT) or the cardiac troponin I (cTnI). These proteins may be detected within the first 3-4 hours of myocardial necrosis. Its sensitivity is close to 100% within 8-12 hours form the beginning of the clinical syndrome.

In addition to its diagnostic utility for myocardial necrosis it also has proved to have short and long range prognostic value in patients presenting with non-STE ACS. This was proved in a meta-analysis (20) of a total of 13 studies with non-STE ACS in which cardiac troponin (T or I) were associated to higher mortality, with 6.4% in those with positive troponin compared to 1.9% in those with negative troponin (RR=3.9). The grade of troponin elevation has also been correlated with higher risk of mortality (21), even with values lower than required for diagnosis of MI or with normal CK-MB.

Recent investigations have indicated that increases of biomarkers upstream from biomarkers of necrosis (cardiac troponins) may provide earlier assessment of overall patient risk and aid in identifying patients with higher risk of an adverse cardiac event.

Some of these upstream biomarkers identified and under consideration include: inflammatory cytokines, cellular adhesion molecules, acute-phase reactants, plaque destabilization and rupture biomarkers, biomarkers of ischemia and myocardial stretch.

B-type natriuretic peptide (BNP) is a neurohormone that is produced in the cardiac ventricular muscle usually related to muscle stretch as with chamber dilatation or pressure overload that correlates with presence of heart failure and ventricular dysfunction. It has also proved to be a useful independent predictor for risk stratifying patients that present with an ACS (22). BNP was found to correlate with the risks of death, MI recurrence and heart failure. Its capacity to risk stratify was universal for all the presenting subsets: UA, NSTEMI and STEMI.

Inflammatory markers such as the highly sensitive C-reactive protein (hs-CRP) (23) and the CD-40L (24) have been found to correlate with increase risk of adverse cardiac events in patients presenting with ACS. However, there is still debate if this is only a marker of the vascular inflammation or if they are directly responsible for mediating plaque instability. CRP elevation has been found to correlate with increase cardiac risk in patients with stable and unstable angina, but not with acute MI. In this last group the CRP may increase related to the inflammatory process resulting from the myocardial necrosis as an acute phase reactant.

The combination of these markers in a punctuation system has also been shown to add predictive value. Sabatine and his collaborators (25) evaluated the 30-day mortality risk associated to the presence of positive or abnormal troponin-I, CRP and BNP. They found that the relative risk (RR) increased with the punctuation score. Upon analyzing this score in the TACTICS TIMI-18 the RR of 30-day mortality increased from 1 in the 0-points group, to 2.1 in the 1-point group, 5.7 in the 2-point group, and 13 in the 3-point group ($P < .001$).

In fact this multimarker strategy has been broaden even more by Marrow and Braunwald (26), were they suggested to measure 5 independent adverse markers that include: myocardial necrosis with cardiac troponin; hemodynamic alteration with BNP (and likely indirectly with CHF upon physical exam); inflammation with CRP or CD-40L; accelerated atherosclerosis with insulin resistance measured by altered fasting blood sugar or glycosilated hemoglobin; and vascular damage assessed by microalbuminuria. It is likely that in a near future we might be using a multimarker punctuation risk score with specially designed point of care kits for easy and faster measuring of these markers for cardiac risk assessment.

Another important variable to add to this multimarker strategy is the presence of ongoing ischemia. The conventional method for detection of ischemia is by evidence of dynamic ST segment changes on ECG or evidence of a new wall motion abnormality by echocardiography or perfusion defect by nuclear imaging. Another promising test for indirect assessment of myocardial ischemia is the evaluation of ischemia modified albumin (IMA). The presence of ischemia affects the ability of the N-terminal region of human albumin to bind cobalt. This may be measured after a set amount of cobalt is injected to the patient and finally assessing the amount of unbound cobalt through colorimetric essays. This test was recently approved by the Food and Drug Administration (FDA) for the diagnosis of ischemia specifically related to ACS. It has the advantage of providing early positive results and before the elevation of cardiac markers from myonecrosis. This assay is reported positive within minutes of ischemia and remains so for up to several hours later, allowing detection before the development of myocardial necrosis (as evidenced by normal levels of creatinine kinase isoenzyme [CK-MB] and troponin). This improved ability to detect ischemia before myocyte destruction would allow for earlier and more accurate management decisions for patients suspected of having an ACS with initial negative ECG and troponin test.

The individual and combined sensitivity of IMA with ECG and cTn was assessed by Sinha and collaborators (27), upon evaluating a total of 208 patients that presented to the ED within three hours of acute chest pain. In the whole patient group, the sensitivity of IMA at presentation for an ischemic origin of chest pain was 82%, compared with 45% of ECG and 20% of cTnT. IMA used together with cTnT or ECG, had a sensitivity of 90% and 92%, respectively, while all three components present had a 95% sensitivity. In a broader meta-analysis conducted by Peacock and his collaborators (28), a total of 1,613 patients that were evaluated with IMA, ECG and cTn within 3 hour of chest pain presentation. This triple test was positive if any single test was positive, and negative if all 3 were negative. The reported sensitivity and negative predictive value for an ACS diagnosis was 95% and 97% respectively. From this meta-analysis a total 1,197 patients had a 6mo follow-up reported. The sensitivity and negative predict value assessed for follow-up adverse outcomes was 87% and 94% respectively. For this reason it may help rule-out an ACS when the initial ECG and troponin test are negative and the clinical presentation is atypical or of mixed characteristics in the presence of low levels of free cobalt. This negative triple test may allow early disposition, rather than a prolonged ACS evaluation in the ED or as inpatient.

TIMI Risk Score

There are different known schemes for predicting adverse cardiac risk according to a punctuation scale. The most renown is the TIMI risk score created by Antman (29) from a multivariate analysis of patients with non-STE ACS (TIMI-11B). This punctuation system was designed to predict the risk of death, non-fatal MI or urgent revascularization within 14 days of presentation. The seven independent predictors were: 1) age > 65 years, 2) the presence of at least three risk factors for CAD (diabetes mellitus, hypertension, hyperlipidemia, smoking or family history of premature CAD), 3) prior coronary angiography with a known coronary stenosis of >50%, 4) use of aspirin within the 7 preceding days form the clinical presentation, 5) at least two angina events in less than 24 hours, 6) ECG

ST segment deviation of > 0.05mV, and 7) increase of cardiac markers.

The percent of cardiac endpoints increased with the TIMI score punctuation: 4.7% for a punctuation of 0 or 1, 8.3% for 2, 13.2% for 3, 19.9% for 4, 26.2% for 5, and 40.9% for a score of 6 or 7. This punctuation system has also been validated in other three clinical studies: the ESSENCE (30), PRISM-PLUS (31) and TACTICS TIMI-18 (32). In these trials of non-STE ACS the TIMI risk score proved to help assess the benefit of more aggressive anticoagulant therapy such as low molecular weight heparin, GP IIb/IIIa receptor inhibitors and an invasive coronary evaluation strategy (respectively) with the increase of the score.

Conservative Strategy versus Invasive Evaluation

The conservative strategy, or guided by ischemia, implies an optimization of the medical therapy during a phase of observation or "cooling" from the acute coronary process. If during this period of time the patient remains free of angina, without complications or without high risk criteria (described ahead) then we may proceed with this conservative approach of evaluation with a non-invasive stress test (preferably as inpatient). If the patient clinically deteriorates or the stress test results positive for ischemia, then further evaluation with coronary angiography may be contemplated. The advantage of this approach is that it helps to limit excessive use of cardiac catheterization and possibly unnecessary revascularization, costs and complications associated.

The invasive strategy consists of an early evaluation with cardiac catheterization with the intention to identify severe CAD that may benefit from sooner surgical or percutaneous intervention. The extent of CAD has known to have prognostic value. For this reason CAD has been classified as: single-vessel disease, two-vessel disease, three-vessel disease and LM disease. In the CASS registry of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 91% compared with 74% for those with one-vessel disease, 59% for those with two-vessel disease, and 40% for those with three-vessel disease (p less than 0.001) (33). Another angiographic finding suggestive of higher risk are those suggestive of plaque instability, such as with evidence of an ulcerated plaque, thrombus, irregular borders or dissection. However, the severity of lesions is not predictive of plaque stability; two thirds of patients with acute MI have less than 50% diameter stenosis at the site of plaque rupture before MI. Another known limitation with coronary angiography is that it is known to underestimate plaque burden, possibly because of vascular remodeling and the diffuse nature of the disease in some cases. Adjunctive use of intravascular ultrasonography has been recommended to facilitate further investigation of hazy lesions on coronary angiography that may result from calcium, thrombus, severe eccentric lesion, or dissection.

Some of the randomized trials that have proved benefit from this invasive strategy include: TIMI IIIB, FRISC II, RITA 3, and the TACTICS-TIMI 18 (4). The patients that benefited the most from straight catheterization were the patients with ST segment depression on the EKG and/or those with cardiac troponin elevation. In the FRISC II, the patients managed with invasive therapy had a significant reduction in death and MI (13.2% versus 22.1%). While the patients in the TACTICS-TIMI 18 the benefit from a reduction in death, MI or re-hospitalization from ACS was 19.5% versus 15.9% in 6 months (p=0.025).

As mentioned previously, coronary angiography is the study of choice in patients with refractory angina or high risk criteria (Table 2) for the development of adverse cardiac outcomes, as recommended by the ACC/AHA 2002 guidelines (4). Some of these high risk features include: age >75 years; resting chest pain of more than 20 minutes duration; physical exam with CHF findings, hypotension or new mitral regurgitation associated with chest pain; EKG with dynamic ST segment changes or ventricular tachycardia; or the elevation of cardiac markers (troponin). Other indicators of high risk that benefit from straight invasive evaluation include: a TIMI score ≥5, left ventricular systolic dysfunction of <40%, a percutaneous coronary intervention in less than 6 mo, prior coronary bypass surgery, or the presence of high risk feature on a non-invasive stress test.

Another important aspect of this risk analysis is that related to possible complications from the cardiac catheterization or from subsequent coronary intervention. The final decision should include into consideration the patient's comorbidities and his preferences. Particularly if he is of advanced age, fragile, has active cancer or terminal disease, or is considered inoperable. The comorbidities known to be associated to increase risk with this invasive approach include: presence of peripheral vascular disease, renal insufficiency, severe left ventricular systolic dysfunction, decompensated CHF, severe obstructive lung disease or known dye allergy. Also, if the coronary anatomy is already known to be severe or not amenable for intervention, then the conservative approach should be favored.

CAD is significant when we find obstructive lesions of >70% stenosis of the lumen diameter of the principal arteries (left anterior descending-LAD, the circumflex-LCX, or the right coronary artery-RCA) or >50% stenosis of the

left main (LM) coronary artery. The revascularization option will depend on the extension of the CAD, type of lesions, distal targets, presence of ischemia and viability. In general, for those with symptomatic single vessel CAD of appropriate characteristics a percutaneous coronary intervention (PCI) is recommended. Multivessel PCI (compared to bypass surgery) may be an option if the patient is not diabetic and the lesions are considered appropriate for intervention. The use of bare metal stents has known to decrease the frequency of restenosis, but still, it is associated with the need for subsequent interventions without difference in survival when compared to bypass surgery. However, there is no data comparing the use of drug eluted stents with anti-proliferating agents (known to have a significant lower rate of restenosis) with that of bypass surgery. Whereas, coronary artery bypass surgery (CABG) is the treatment of choice in patients with LM stenosis (>50%), CAD with 3 vessel disease (≥50%), or 2 vessel disease if there is proximal LAD stenosis of >70%, predominantly in view of its known long term mortality reduction besides the benefit of symptom (angina) reduction, compared to medical therapy (34). These benefits are most notable in patients with worse left ventricular function and/or with severity of ischemia.

Non-Invasive Evaluation of Ischemia

The selection of a non-invasive evaluation for ischemia is fundamentally based in the patient characteristics, his pre-test probability to have CAD, his capacity to walk on a treadmill, his baseline ECG, and the local availability and capacity for interpretation of these tests. The stress test options vary regarding its diagnostic capacity (sensitivity, specificity and predictive value). They also vary according to prognostic value, costs and inter-observer variability. The non-invasive studies may be classified according to the type of CAD that it pretends to detect: anatomic information of CAD, reversible myocardial ischemia, or an old MI. These tests may be subdivided according to their method of detecting ischemia (ECG changes, perfusion defects or wall motion abnormalities) and the method used to induce ischemia (exercise or pharmacologic stress). The grade of ischemia may also be estimated semi-quantitatively by each of these methods. With exercise stress test ischemia may be diagnosed by the development of ST segment depressions on ECG, however, they do not necessarily localize the ischemic territory. While the presentation of ST segment elevations during stress ECG does localize the ischemic territory, however it occurs infrequently and usually correlates with critical high-grade lesions or that related to coronary spasm. On the other hand the use of cardiac images, localize the ischemic territory, demonstrated by perfusion defects (with nuclear images) or with regional contractility alterations (with echocardiography). Ischemia on multiple vascular territories usually implies a worse prognosis and the possible benefit from a more aggressive management including the use of coronary angiography. The presence of an old MI is a very specific diagnostic marker for presence of CAD. This may be suggested or confirmed by: 1) evidence of a pathologic Q waves, of more than 40ms in more than 2 contiguous ECG derivations at rest, 2) by the presence of a segmental decrease or absence of wall motion contractility (seen by echocardiography, magnetic resonance imaging [MRI], contrast ventriculography or nuclear gated images), or 3) by the presence of a fixed myocardial perfusion defect with nuclear images.

In summary, the diagnostic and prognostic non-invasive tests available for the assessment of ischemia are the following:

- Regular stress test with ECG.
- Regular stress test with ECG combined with ancillary cardiac imaging studies (nuclear or echocardiographic).
- Pharmacologic "stress test" with ECG combined with ancillary cardiac imaging studies (nuclear or echocardiographic).
- Cardiac magnetic resonance imaging and electron beam computed tomography (still in evolution and not discussed in this article).

Table 4 illustrates the different individual factors to take in to consideration for the selection of the appropriate non-invasive evaluation for the diagnosis of myocardial ischemia.

Pre-test Probability of CAD

The initial estimation of CAD probability based on the clinical history determines the need for additional diagnostic tests. This estimation is known as the pre-test probability and may be viewed as prevalence. When a diagnostic test is done, the sensitivity and the specificity should be combined with the pre-test risk to determine the probability of ischemia post-test. For patients with a high pre-test probability, a positive test is highly predictive of ischemia, but a negative test does not exclude CAD. On the other extreme, in the patient with a low pre-test probability, a positive test is possible to represent a false positive result. However, if the test is negative, this result is highly predictive of absence of CAD. In summary, the

Table 4. Deciding the Optimal Stress Test to Use

	Treadmill	Echo	Thallium	Sestamibi
Goal of test:				
- LVEF	No	Yes	No	Yes
- Screening test	Yes	Yes	Yes	Yes
- Low cost desired	Yes	Fair	No	No
- Post MI viability	No	Yes	No	Yes
Patient factors:				
- Obesity	Yes	Yes	No	Yes
- Female	No	Yes	No	Yes
- Large chest	Yes	No	Yes*	Yes*
- COPD	No	Yes	Yes	Yes
- Uncontrolled HTN	No	Yes	Yes	Yes
ECG factor				
- LBBB	No	No	Yes	Yes
- Baseline ST changes	No	Yes	Yes	Yes
- LVH, PPM	No	No	Yes	Yes
- Irregular rhythm (Afib., PVC's)	No	Yes**	Yes	Yes
Can not exercise	No	Yes	Yes	Yes

LVEF= left ventricular ejection fraction, COPD= chronic obstructive Pulmonary disease, LBBB= left bundle branch block, Afib.= atrial Fibrillation, PVC= premature ventricular contractions

*If presence of BA, adenosine and dipyridamole is contraindicated, most use dobutamine.

**If rate is controlled, exercise echocardiography may be considered. Dobutamine echocardiography or perfusion imaging should be avoided if frequent PVC's or uncontrolled fast atrial fibrillation.

probability of CAD after a stress test is directly related to the specific population (patient) evaluated and the results of the test. Diamond and Forrester (36) analyzed the angiographic and/or the pathologic data of 28,000 patients and they estimated the probability of CAD based on the age, sex, and the character of the chest pain (Table 5). The chest pain was characterized in 3 groups: 1) typical or definitive angina, described by all the following: a substernal pain with the typical quality and duration, provoked by effort or emotional stress, and that it improved with rest or nitroglycerine; 2) atypical or probable angina: chest pain with only two (from three) of the above mentioned characteristics; 3) chest pain not ischemic: with only one or none of the above mentioned characteristics. The typical or definitive chest pain of ischemia makes the pre-test probability for CAD very high, so that the results of a diagnostic test will not alter dramatically the probability of CAD. However, in certain circumstances a study may be realized for a different purpose, such as: to localize the ischemic territory, for prognostic stratification, or even for functional capacity or to assess the response to a specific therapy. In the case of a 50 year old male with atypical or probable angina, he has a 50% probability to have CAD (Table 5). This is precisely the patient that most benefits from the diagnostic evaluation, the patient with an intermediate probability, because the results from the test have a higher predictive value.

Regular Stress Test

This test may be done either walking on a treadmill or by riding a static ergonometric bicycle. The treadmill test is the most popular alternative; since the people are more adapted to walking than to riding a bicycle and (generally) they accomplish a better stress yield. It is the study of choice because of its simplicity, low cost, availability and global familiarity. There are multiple exercise protocols to select according to the patients physical capacity and the purpose of the test. The Bruce protocol offers the best diagnostic value and is very useful for the assessment and prognosis of CAD. This protocol starts with a speed of 1.7 miles per hour (MPH) and an inclination of 10 grades that corresponds to oxygen consumption of 5 metabolic equivalents (METS). A MET refers to the resting volume oxygen consumption per minute (VO_2) for a 70-kg, 40-year-old man. One MET is equivalent to 3.5 mL/min/kg of body weight. Every 3 minutes it changes in stage, with an increase of speed and grade equivalent to an increase of 3 METS in work. The goal of the diagnostic test is for the patient to reach his maximum aerobic capacity, reaching his highest heart rate for exercise. The increase in oxygen demand is proportional to the rate-pressure product, that is, the product of heart rate and systolic blood pressure. Because the increase heart rate is primarily responsible for the increased oxygen demand, adequacy of exercise response is judged on the basis of heart rate achieved during exercise. An exercise test is considered adequate if 85% or more of the age-adjusted maximum heart rate (MHR) is achieved, also known as the target heart rate (THR). The maximum heart rate (MHR) may be estimated according to the age of the individual.

Table 5. Pre-test Probability of Coronary Disease in Symptomatic Patients According to Age and Sex*

AGE (years)	Non-Angina Chest Pain		Probable Angina (or Atypical)		Typical Angina	
	M	F	M	F	M	F
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

M= masculine, F= female

*Each one of these values represents the percent of patients with CAD by coronary angiography. Adapted by the AHA/ACC guidelines if chronic angina, 2000.

MHR= 220- patients age, or 200- (0.63 x patients age)
(THR) = (MHR) x 85%

Another reference for adequacy of stress is a double product above 25,000 (assessed from the product of the highest heart rate and the maximal systolic pressure). In summary, the diagnosis of ischemia is done when the ST segment depresses more than 0.1 mV, 60 ms after the J point, either horizontally or down slopping, or with the elevation of the ST segment ≥ than 0.1mV with or without the classic chest pain. In the patient that presents with an ACS, if he is considered low risk, he may be walked on the treadmill after 8-12 hours free of chest pain or congestive heart failure. While intermediate risk patients may be evaluated with exercise stress two days from his presentation.

Contraindications to exercise stress testing according to the ACC/AHA 2002 guidelines are:

Absolute Contraindications:

- Acute myocardial infarction (within 2 days)
- Unstable angina not previously stabilized by medical therapy, without evidence of high risk features or recurrence of angina within 8-12 hrs.
- Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Acute aortic dissection

Relative: Relative contraindications (can be superseded if the benefits of exercise outweigh the risks).

- Left main coronary stenosis
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities
- Severe arterial hypertension: In the absence of definite evidence, the committee suggests an SBP of greater than 200 mm Hg and/or a DBP of greater than 110 mm Hg.
- Tachyarrhythmias or bradyarrhythmias
- Hypertrophic cardiomyopathy and any other forms of outflow tract obstruction
- Mental or physical impairment leading to an inability to exercise adequately
- High-degree atrioventricular (AV) block

An extensive meta-analysis of treadmill stress test (with 24,000 patients) revealed that the average sensitivity and specificity was 68% and 77% respectively (36). The sensitivity to detect severe CAD (multivessel or LM stenosis) was an average of 86%.

The findings associated to a higher risk of adverse cardiac events and with an annual mortality that exceeds 5%, are the following (7, 37):

- Inability to complete 6 minutes of a Bruce protocol
- Ischemia at a low heart rate (≤120 beat/min)
- Early positive test results (≤3 min)
- Strongly positive test results (≥2 mm ST depression)
- Sustained ST segment depression ≥3 minutes after cessation of exercise
- Down-sloping ST segment depression
- Flat or lowered blood pressure (BP) response. Inability to increase the systolic BP ≥120 mmHg or a sustained decrease ≥10 mmHg or lower than baseline with progressive exercise
- Serious ventricular arrhythmia

Various punctuation systems have been developed for prognosis assessment. They take into consideration the grade of ST segment depression and the exercise duration. The most popular was developed by Duke and his collaborators (38, 39), called the "Duke Treadmill Score" (DTS).

DTS= Exercise duration (minutes, in Bruce protocol) - 5 x (maximal ST segment depression, in mm) - 4 x (the angina index).

The angina index is valued from 0-2 according to the presence and severity of angina: 0 if no angina is provoked, 1 if angina does not limit the exercise and 2 if angina is limiting. The patient is then stratified according to the final score: low risk if ≥5, moderate risk if the score is between -10 and 5, and high risk if the score is ≤-11. The annual cardiac mortality increases with the risk: 0.25% in the low risk, 1.25% in the moderate risk and 5.25% in the high risk. However this prognostic information was based on outpatients with suspected CAD and not in patients with ACS.

Another dilemma is whether patients with normal exercise ECGs gain any benefit with myocardial perfusion imaging (MPI). A study by Mattera and colleagues (40) evaluated 313 patients who had normal resting ECGs and underwent exercise MPI. They concluded that patients at low to intermediate risk of CAD per the criteria of Diamond and Forrester (35) gained no benefit and had no adverse events if the exercise ECG was normal. However, those

with abnormal stress ECGs and those with high pre-test risk gained benefit from MPI. For this reason they suggested that the use of this "stepwise" approach of the baseline ECG and the pre-test risk is cost-effective.

Stress Testing with Cardiac Imaging

Cardiac imaging is useful in cases were the patient has baseline ECG changes or is using digoxin that may affect the diagnostic capacity of the treadmill ECG test for assessment of ischemia. The ECG changes associated with false positive results include: resting ST segment depression of >1 mm, complete left bundle branch block (LBBB), ventricular pacing rhythm, preexitation (Wolff-Parkinson-White) syndrome, or left ventricular hypertrophy (LVH) with strain pattern (7). Exercise ECG has also been associated with a poor positive predictive value and higher incidence of false positive results in women (7, 41). For these specific situations or subgroups, the use of ancillary cardiac imaging modalities will help increase predictive value, sensitivity and specificity. The two current imaging options are nuclear or by echocardiography.

MPI is done with either exercise or pharmacologic stress. In addition to the choice of stress modality, radionuclide selection is also important. The current radionuclides available include thallium-201 (TL-201) or technetium-99m (Tc-99m) either sestamibi or tetrofosmin, that measure myocardial perfusion. These radionuclides incorporate within the myocardial cell according to the blood perfusion. Typically, exercise MPI seeks to uncover areas of infarction or ischemia by comparing the perfusion of the heart at a resting state versus a stressed state. Areas that show decreased perfusion at both stress and rest are indicative of MI scar, whereas areas with normal perfusion at rest but decreased perfusion at stress are indicative of myocardial ischemia. The specific area with a perfusion abnormality indicates the involved coronary artery, and the extent of perfusion abnormalities correlate with the severity of CAD. These nuclear images may be planar (3 fixed positions) or with a single photon emission computed tomography (SPECT) technique, that take images 180° with 3-dimentional reconstruction, that allow visual or quantitative technique analysis. Of the two radionuclides available, the Tc-99m produces better images in view of a higher photon energy and shorter half-life, allowing larger doses. These advantages are somewhat offset by less myocardial extraction, increased uptake in abdominal organs, and lack of redistribution. It is preferred in obese patients (>100 kg) and in women to help decrease the artifacts from breast attenuation. It is also different to Tl-201 by not redistributing since it binds irreversibly to the intracellular mitochondria. For this reason Tc-99m may be used to localize ischemia upon dealing with mixed characteristic or atypical chest pain. The patient may be injected in the moment of resting pain, equivalent to the "stress", and it will incorporate within the regions with adequate perfusion and it will remain without redistributing. This will enable us to treat the patient and perform the images subsequently to be compared with new resting images.

The average sensitivity and specificity of Tl-201 SPECT with exercise, is 90% and 80% respectively (42). The SPECT technique generally is more sensitive than the planar images for the diagnosis of CAD, to localize vascular territories and to predict multivessel disease. Stratman and his colleagues evaluated 126 patients with exercise Tc-99m before discharging patients admitted with UA/NSTEMI. After 12 months of follow-up, the only independent predictor of cardiac events was the presence of reversible perfusion defects, with a relative risk of 3.8 (43).

Echocardiographic images help assess myocardial wall motion (systolic thickening) both at baseline (rest) and after exercise, to identify regional alterations of contractility after stress indicative of ischemia. This wall motion abnormality is visually quantified according to the degree of thickening: normokinesia (normal movement), hypokinesia (decrease movement), akinesia (absence of movement), or diskinesia (paradoxical movement). Exercise echocardiography (EE) should be performed for patients who can exercise. Advantages include that it is a less expensive test (compared to nuclear imaging) with good specificity for identifying ischemic territories. It also can be used to assess the severity of valvular dysfunction. There has been increasing interest in the supine bicycle test, because it allows for imaging at peak exercise rather than immediately after peak exercise. For the patient unable to exercise, a dobutamine stress test can be performed. A biphasic response with dobutamine, in which contractility initially increases with lower doses of dobutamine and then decreases with higher doses, is diagnostic of ischemia. Dobutamine echocardiography (DE) also is useful to assess myocardial viability. The most significant limitations of stress echocardiography are image quality (in some patients), especially after exercise, and the experience of the interpreter greatly influence the accuracy of the test. Image quality may be improved with the use of contrast microbubbles for better definition of the subendocardial wall. The reported sensitivity varies between 70-97% with an average of 85% in EE and 82% for DE. The average sensitivity for EE to detect single-vessel disease is 79% and better for multi-vessel disease with 90%. The average reported specificity is 86% for EE and 85% for DE.

Both imaging options (nuclear and echocardiography) increase the sensitivity and specificity of the regular exercise test. Besides its diagnostic value, it also helps us quantify the severity of ischemia and to define ischemic territories and systolic function alterations that may correlate with multi-vessel or LM disease with worse prognosis.

Imaging findings associated with more risk are the following (30, 33):

- Moderate to severe LV systolic dysfunction at rest (LVEF < 35%) or with exercise.
- Stress-induced large perfusion defect (particularly if it involves the anterior wall).
- Stress-induced multiple perfusion defects of moderate size.
- Large, fixed defect associated to ventricular dilatation or increased lung uptake (of thallium-201).
- Stress-induced moderate perfusion defect with LV dilatation or increased lung uptake (of thallium-201).
- Echocardiographic wall motion abnormality (more than two segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min).
- Stress echocardiographic evidence of extensive ischemia.

Pharmacologic Stress Testing with Cardiac Imaging

Pharmacologic stress testing is an available option for patients that can not walk on a treadmill or are unable to tolerate this test related to orthopedic problems, neurologic impairment, peripheral vascular disease, severe chronic obstructive pulmonary disease, or simply by loss of physical fitness (common in the elderly).

Patients taking beta-blockers or other negative chronotropic agents that would inhibit the ability to achieve an adequate heart rate response to exercise are also appropriate candidates for vasodilator stress. The incapacity to undergo an exercise stress test has been found to relate to a higher risk of cardiovascular events. However, these patients may be evaluated with pharmacologic stress tests.

The current pharmacologic alternatives include: adenosine, dipyridamole (persantine), and dobutamine. The first two are vasodilating drugs that should be combined with radionuclide images. While dobutamine is a positive inotropic and chronotropic drug that mimics the physiologic changes during regular exercise and may be combined with either imaging options of echocardiography or radionuclide perfusion.

Adenosine acts through specific adenosine receptors to cause coronary microvascular vasodilatation. Dipyridamole acts by inhibiting cellular uptake of adenosine and increasing availability, which lead to similar biologic effects to adenosine but at a slower onset, longer duration of action and higher patient to patient variability.

This coronary artery vasodilation induced by adenosine or dipyridamole is attenuated in diseased coronary arteries, which have a reduced coronary flow reserve and cannot further dilate in response to adenosine. This is not the case in healthy or less-diseased coronary arteries in the same patient, which produces relative flow heterogeneity throughout the coronary arteries, resulting in relatively more coronary blood flow in the healthy or less-diseased coronary arteries compared with the more-diseased coronary artery. In most cases, coronary blood flow in the diseased coronary arteries does not decrease. However, in cases of severe vessel stenosis or total occlusions with compensatory collateral circulation, a decrease in coronary blood flow may occur in the diseased coronary artery, thus inducing ischemia via a coronary steal phenomenon. This regional flow abnormality may be assessed by perfusion defects during radionuclide imaging.

These agents are not free of side-effects and may be very unpleasant for the patient. With adenosine, approximately 80% of patients experience minor adverse effects from the infusion. They are usually more frequent (compared to dipyridamole) but of shorter duration in view of the very short half life of adenosine (6 seconds), rarely requiring aminophylline (antidote) after discontinuation of the infusion. Adverse effects include systemic effects (dizziness, headache, symptomatic hypotension, dyspnea, and flushing), gastrointestinal effects (nausea), and cardiorespiratory effects (dyspnea, bronchospasm, chest pain, heart conduction block and ST-segment changes). However, an absence of these effects does not imply a lack of efficacy of the adenosine with respect to coronary vasodilation. The chest pain experienced during adenosine infusion is very nonspecific and does not indicate the presence of CAD. First and second degree atrioventricular conduction block may commonly occur, but significant hemodynamic high degree AV block rarely occurs and revert with stopping the infusion. With dipyridamole the adverse effects experienced are similar to those with use of adenosine. While they are less frequent with persantine (47%), they tend to be more serious than those associated with adenosine. In addition, more of the patients require aminophylline for reversal of adverse effects.

Contraindications for adenosine or dipyridamole stress testing:

Absolute:

- Patients with active bronchospasm or patients being treated for reactive airway disease, since it may lead to prolonged bronchospasm, which can be difficult to treat or can remain refractory.
- Patients with more than first-degree heart block (without a ventricular demand pacemaker), since it may lead to worsening of the heart block.
- Patients with a systolic BP of less than 90 mmHg should not undergo adenosine or dipyridamole stress testing because of the potential for further lowering of the blood pressure.
- Patients using dipyridamole or methylxanthines (eg, caffeine and aminophylline) should not undergo an adenosine or dipyridamole stress test because these substances act as competitive inhibitors of adenosine at the receptor level, potentially decreasing or completely attenuating the vasodilatory effect of adenosine. In general, patients should refrain from ingesting caffeine for at least 24 hours prior to adenosine administration.

Relative:

- Patients with a remote history of reactive airway disease (COPD/asthma) that has been quiescent for a long time (approximately 1 y) may be candidates for dipyridamole. However, if a question exists concerning the status of the patients' airway disease, dobutamine stress testing may be the safer choice.
- Patients with a history of sick sinus syndrome (without a ventricular demand pacemaker) should undergo adenosine or dipyridamole stress testing with caution. These patients are prone to significant bradycardia with dipyridamole; therefore, use caution if they are to undergo dipyridamole stress. Similarly, those patients with severe bradycardia (heart rate ≤40 beats/min.) should undergo dipyridamole stress with caution.

The sensitivity and specificity of adenosine or dipyridamole stress with TL-201 SPECT is 89% and 78% respectively. It is considered the preferred alternative for assessment of ischemia in patients with resting LBBB (or during stress) or with a ventricular pacing rhythm. Exercise and dobutamine stress testing has known to produce false positive septal defects in these patients. Also, as mentioned above, this is the preferred non-invasive method of evaluating CAD in the female and the elderly incapable of attaining an optimal exercise effort (THR) for the diagnosis of ischemia.

The benefit of dipyridamole Tl-201 for risk stratification post non-STE ACS was evaluated by Younis and his collaborators (44). They evaluated a total of 68 patients that remained clinically stable after their admission. After an average follow-up of 12 months, the patients with abnormal images had a higher risk of adverse cardiac events than those without, 72% versus 7% respectively.

Dobutamine has some vasodilating effects, but as mentioned above, it's principal effect result from mimicking a regular exercise test. However, the rate-pressure product usually is lower than that from exercise testing. As we increase the infusion dose in a step-wise fashion, this leads to an increase of heart rate, blood pressure and cardiac contractility that may lead to provoke ischemia. It is the usual alternative drug for stress testing with perfusion imaging, in case adenosine or dipyridamole are contraindicated in view of BA. Its sensitivity is lower, likely related to a failure of reaching the THR. There are different dobutamine infusion regimens, but the usual top dose is 40 mcg/kg/min followed by atropine or handgrip as adjuncts to achieve this THR.

Resumen

Los pacientes hospitalizados con angina inestable (AI) o infarto miocardico sin elevación del segmento ST (IMSEST), están ha riesgo de sufrir recurrencia de infartos, angina refractaria, y muerte. Estos pacientes necesitan de una evaluación más agresiva. De acuerdo con las guías publicadas por el panel de la ACC/AHA en pacientes con AI/IMSEST, estos se deben categorizar en una escala de riesgo (de subsecuentes eventos adversos) como: bajo, intermedio o alto. Esto se debe hacer por la evaluación inicial de: ECG, el historial clínico, el examen físico, y los marcadores cardíacos. Entre los marcadores cardiaco asociados a estratificar riesgo esta la troponina cardiaca (I & T), el péptido natriuretic tipo B, la proteína-C reactiva y el CD 40L. También se debe utilizar el "TIMI risk score" complementario a este análisis de riesgo. Los pacientes identificados como de alto riesgo, si no tienen contraindicaciones, se deben manejar y evaluar agresivamente con angiografía coronaria. Luego de evaluar la anatomía y la severidad de su enfermedad coronaria es que se decide si se beneficia de otra intervención percutánea o quirúrgica. En los pacientes de riesgo inicial bajo y algunos de riesgo intermedio, se recomienda una evaluación conservadora, que incluye una prueba intra-hospitalaria no-invasiva para isquemia y de función cardiaca. Esta prueba no-invasiva también nos puede ayudar a identificar pacientes con anatomía coronaria de más riesgo que también se puedan beneficiar de cateterismo cardiaco. La determinación de la prueba no-invasiva optima, va depender de varios factores: capacidad

para caminar en la polea, su ECG de base (que no interfiera con su capacidad para diagnosticar isquemia), presencia de LBBB, probabilidad pre-prueba de enfermedad coronaria, características del paciente (sexo, obesidad, COPD y asma), la disponibilidad del estudio y la pericia con el estudio. En aquellos con una probabilidad pre-prueba alta de enfermedad coronaria, se debe considerar un estudio de ejercicio con imágenes ancilares, como prueba de elección, ya que añade información pronóstica para el paciente. En aquellos, con una probabilidad pre-prueba baja para enfermedad coronaria, entonces se debe considerar el uso de la prueba regular de ejercicio con ECG. Mientras que los pacientes (en general) que no se pueden evaluar con ejercicio (por condiciones médicas o físicas), deben ser evaluados con pruebas farmacológicas (preferiblemente por adenosina o dipiridamole) combinada con imágenes de perfusión. Finalmente, basado en los resultados de estas pruebas es que se determina si se requiere de cateterismo cardiaco adicional. En general, los pacientes con pruebas de perfusión negativa tienen un pronóstico excelente.

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