

AIR *STUDY*

(ANGINA INSTABILE RAFFREDDATA)

**RISK STRATIFICATION OF PATIENTS
AFFECTED BY ACUTE CORONARY
SYNDROMES WITHOUT ST-SEGMENT
ELEVATION**

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BACKGROUND

Risk stratification in patients affected by unstable angina (UA) is difficult because the correspondence between clinical aspects and culprit lesion severity, coronary artery disease extension, clinical course toward stabilisation is often elusive.

The major clinical determinants during hospital phase are both refractoriness to therapy and the amount of jeopardised myocardium (i.e. the site of the culprit lesion). The total “coronary atherosclerotic burden” (i.e. multivessel disease) and the left ventricular function are factors more likely linked to mid and long term prognosis, as after an acute myocardial infarction. In addition, the prognosis depends also on the progression of the disease (about in one third of patients within one year, often multifocal).

Guidelines for treatment of patient with UA are not so definite as for acute myocardial infarction. This due to two opposite strategies, conservative and invasive, are currently adopted by clinicians, according to the country and to the single centre facilities for myocardial revascularisation. Invasive strategy aims at the early treatment of the culprit lesion with PTCA or CABG, with no respect to clinical course and to residual ischaemia. Conservative strategy, likely in AMI patients, deserve myocardial revascularization to patients with refractory or residual inducible ischaemia.

The few studies comparing these strategies (TIMI IIIB, VANQUISH, OASIS Registry, TIMI IIIB Registry) have no demonstrated any superiority in terms of major clinical outcome (death, non fatal AMI), even if patients treated more conservatively showed during follow-up more hospitalisation due to recurrent ischemia and related invasive procedures.

Randomised studies however present the following limitations:

- 1) in the organiser country, U.S., most of patients undergo routinely to coronary angiography
- 2) there is a high cross-over rate between the two groups; this doesn't allow to define a superiority of one therapy instead of one strategy.
- 3) The definition of *acute coronary syndrome without ST elevation* recently adopted in clinical trials, despite represents an advantage over the past, still groups diseases with different pathophysiology (e.g. unstable angina with transient ST elevation/aborted Q-MI and unstable angina with diffuse ST depression e subendocardial necrosis/true nonQ-MI)

From the practical point of view is therefore difficult to extrapolate definite guidelines for the clinical practice. Particularly is not stated which subgroups of patients may benefit from coronary angiography and revascularization procedures, and which functional tests can better stratify patients with cooled-off symptoms (up to 50% in Braunwald subgroups).

AIM OF THE STUDY

- The study is targeted towards patients at intermediate and low risk, who frequently don't develop complications during the clinical course. The principal aim of the study is to develop a risk stratification strategy based on the assessment of residual ischaemia in stabilised patients. Two non invasive tests, exercise stress test and stress echo with dobutamine, will be compared to assess the respective predictive power in detecting patients at low risk of major future events (death, myocardial infarction, myocardial revascularization procedures). This should lead to an optimal use of invasive diagnostic and revascularization procedures.
- Secondary aim is to study the ischaemic threshold at 4-8 weeks from acute phase, to detect possible variations due to remodelling of the culprit lesion.

DESIGN OF THE STUDY

The study is a randomised and multicenter one.

Hospitalised patients with stabilised unstable angina, undergo an ischaemic provocative test with exercise test (ET) or with dobutamine stress echocardiography (DASE). Patients with clinical or echographic signs of left ventricular failure and large jeopardised myocardium directly undergo to coronary angiography.

According to the results, patients are classified as follow:

- high risk patients perform coronary angiography and revascularization if necessary (CABG or PTCA)
- patients at intermediate risk perform coronary angiography and in absence of threatening coronary lesions follow a medical treatment
- low risk patients are treated conservatively

The last two groups repeat the test (ET or DASE) after 4-6 weeks.

POPULATION OF THE STUDY

Males and females aged 70 ys. or less admitted to Cardiology Department (not necessarily to CCU) with typical symptoms of unstable angina (classes IB-IIB-IIIB Braunwald) and:

- new ischaemic ECG changes, persistent or transient, in two or more leads (negative T waves, ST depression > 1mm at J+80 msec, ST elevation > 1 mm for less than 20 minutes)
- history of ischaemic heart disease documented by clinical reports, invasive or non invasive tests

Patients, not on i.v. nitrates, are randomised after 24 hours free from angina and/or silent ischaemic ECG changes.

EXCLUSION CRITERIA

- Persistent ST segment elevation and/or fibrinolytic therapy on admission.
- myocardial infarction (Q-AMI or nonQ-AMI) defined by chest pain > 30 minutes, typical ECG changes and CK rise > 2 times upper limit.
- Braunwald class C post infarction angina (within 2 months)
- signs or symptoms of heart failure at admission or during hospital course
- severe left ventricle impairment (hypo-akinesia of 6/16 segments or EF<30%)
- PTCA in the previous 6 months or CABG in the previous 12 months
- patients in whom a coronary angiography or revascularisation has already been planned
- inability to perform the exercise test
- atrial fibrillation, left bundle brunch block, depolarisation abnormality due to left ventricular hypertrophy or digitalis
- poor acoustic window

AMPIEZZA DEL CAMPIONE E ANALISI STATISTICA

La numerosità dei pazienti è stata calcolata per poter identificare una differenza di 20 punti percentuali (con potenza beta 0.80 e significatività alfa 0.05) tra le due metodiche in termini di specificità per gli end-points hard a 6 mesi, assumendo per la metodica peggiore una specificità del 75%. Il numero dei pazienti richiesti così calcolato è di circa 700 per braccio di randomizzazione.

I risultati dello studio verranno analizzati allo scopo di determinare sensibilità, specificità, poteri predittivi dei test funzionali eseguiti, sia separatamente che dopo aggiustamento per le variabili clinico-strumentali di confondimento.

DETAILS OF THE STUDY

RECOMMENDED PHARMACOLOGICAL TREATMENT

Pharmacologically treatments for patients with unstable angina are described in Clinical Practice Guideline – Unstable Angina: Diagnosis and Management (AHCPR publication No. 94-0602), also summarised in *Circulation*, 1994;90:613-622.

We recommend the shift from i.v. nitrates to oral formulation after 24 hours without symptoms to allow early randomisation (see inclusion criteria). For class I patients i.v. nitrates are not mandatory.

Recent studies (FRISC, ESSENCE, FRIC) have demonstrated that low molecular weight heparin (LMWH) are an alternative to unfractionated heparin in unstable angina.

RANDOMISATION

After 24 hours on oral treatment without refractory angina (defined as episodes with new ECG changes or lasting >20 minutes) and without silent ischaemic episodes at ST-T monitoring (total ischaemic burden > 20 min/24 hours), patients are randomised to exercise test (ET) or to dobutamine-atropine stress echocardiography (DASE).

Randomisation is done using a numerical sequence, in closed envelopes.

For those patients who present after randomisation refractory angina recurrences, clinicians are free to decide on clinical bases to wait for a new stabilisation or to go directly to invasive procedures. In the last case the patient will not undergo functional examination with ET/DASE, but nevertheless will be followed-up.

ISCHAEMIC ECG MONITORING

Eligible patients with UA are monitored for ST-T ischaemic episodes with the device usually employed in each Centre (i.e. CCU monitor, dedicated monitoring systems, Holter, ...), carefully choosing the leads most involved at admittance (of course not in case of 12 lead ECG system).

In patients either with persistent ischaemia or for whom an aggressive strategy is planned, ischaemic monitoring is prolonged according to physician judgement.

An ischaemic episode is defined by an ST amplitude shift of at least $\pm 100\mu\text{V}$ from baseline in any one of 12 leads occurring within 10 minutes and persisting for at least one minute.

The episode is over when ST segment goes back to baseline boundaries ($\pm 100\mu\text{V}$) for at least one minute. Episodes thus are considered single when separate by one minute.

Is strongly recommended that the quality of monitoring is optimal to reduce at most artefacts. A good preparation of the skin with gentle brushing, cleaning with isopropyl alcohol, refreshment of electrodes every 24 hours guarantees good results.

EXERCISE TEST

Exercise test is performed at the treadmill according to Bruce protocol, without therapy discontinuation and symptom limited. Alternatively, bicycle exercise test with scalar protocol of 25 watts every 3 minutes is permitted.

Diagnostic criteria for myocardial ischaemia is ST depression (downsloping or horizontal) \geq 1 mm at 80 msec. from J point in three consecutive beats. Interruption criteria are: strong chest pain, dispnoea or bad tolerated fatigue, worsening ST depression $>$ 2 mm at I° stage, or $>$ 4 mm at any stage, ST elevation (in leads without Q waves) $>$ 1mm in two contiguous leads, absence of increase or fall of blood pressure, hypertensive response (systolic BP $>$ 240, diastolic BP $>$ 120 mmHg), ventricular (premature repetitive ventricular beats, worsening, NSVT, VT) or sustained supraventricular arrhythmia, maximal heart rate.

According to Treadmill Duke Score (TDS) patients are classified in *high* (TDS $<$ -10), *intermediate* (TDS between -10 e 4) or *low score* (TDS \geq 5) with the following formula:

$$\text{TDS} = \text{exercise duration (min)} - (5 \times \text{mm of ST shift}) - (4 \times \text{treadmill angina index})$$

(TREADMILL ANGINA INDEX IS 0= NO ANGINA, 1= NON LIMITING ANGINA, 2= LIMITING ANGINA)

By cicloergometer, exercise duration must be converted into the Bruce protocol one, using the equivalence diagram.

DOBUTAMINE-ATROPINE STRESS ECHOCARDIOGRAPHY

A standard protocol is adopted, starting with 10 γ /kg/min for 10 minutes, with 10 γ /kg/min increases every 3 minutes, up to 40 γ /kg/min. Atropine is added (0.25 mg every minute up to 1 mg) till 85% of teorical maximal heart rate is reached. Interruption criteria are: multiple, severe new wall motion abnormalities, diffuse and marked ST elevation in leads without Q waves, threatening ventricular arrhythmias, sustained supraventricular arrhythmias, severe chest pain, blood pressure reduction of 40 mmHg or more compared to baseline levels, SBP $<$ 90 mmHg o $>$ 220 mmHg.

Test is considered positive with new wall motion abnormalities (NWMA= hypokinetic or akinetic) in two contiguous segments. Analysis is performed offline separately by two blind echocardiographers, possibly on digital recordings. In case of discordance, a third opinion is heard.

Patients are classified as follow: *high score* with NWMA in \geq 4 segments (the whole apex is considered a single segment), *intermediate score* with a positive test at heart rate $<$ 100/bpm, low score with negative test or positive at heart rate $>$ 100 bpm.

CORONARY ANGIOGRAPHY

Cardiac catheterisation is done in patients with high and intermediate score. Coronary anatomy is defined at high risk in presence of multivessel disease with severe proximal stenosis ($>$ 70%) of major coronary arteries encompassing LAD (i.e. proximal right and/or circumflex coronary artery and proximal left anterior descending); main stem stenosis $>$ 50%.

RISK STRATIFICATION

Based on provocative test (ET or DASE) and on left ventricular function (LVF), patients are classified in three RISK CATEGORIES:

♥ LOW RISK

- negative test, independently from ejection fraction
- EF > 40% and low score
 - ⇒ patients are allocated to medical treatment

♥ INTERMEDIATE RISK

- EF > 40% and intermediate score
- EF < 40% and low score
 - ⇒ coronary angiography is indicated, but without *high risk coronary anatomy* patients continue on medical Rx. For high risk coronary anatomy myocardial revascularisation is indicated according to each Centre guidelines.

♥ HIGH RISK

- positive test with high score
- EF ≤40% with intermediate score
 - ⇒ patients undergo coronary angiography and possibly revascularisation (CABG or PTCA) if clinically indicated.

Patients treated medically, and without primary end-points, repeat the functional test possibly without drugs changes (especially beta-blockers) at 4-6 weeks and at the end of follow-up. The result of these second tests are used according to cardiologist's clinical practice, beside any study protocol indication.

FOLLOW-UP

Study duration is of 6 months. PRIMARY END-POINTS at first and sixth month are:

- ♥ cardiac death
- ♥ non fatal myocardial infarction
 - presence of at least 2 of the followings: typical chest pain, new significant Q waves, enzymatic release more than twice the normal upper limit)
- ♥ unstable angina
 - worsening symptoms that lead the patient to the urgent hospital admission and presenting ST-T modification
- ♥ refractory angina
 - recurrence of spontaneous or effort angina, limiting daily activities despite maximal medical treatment (with beta-blockers and/or calcium antagonists -non dihydropyridinic-, ASA, nitrates), leading to coronary angiography or myocardial revascularisation.

SECONDARY END-POINTS is the evaluation of ischaemic threshold after 4-6 weeks from patient discharge, repeating the functional test with the same condition (drug therapy) of the first examination.

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