

COST OF STRATEGIES AFTER MYOCARDIAL INFARCTION

COSTAMI ELDERLY

A COST-EFFECTIVENESS EVALUATION OF INVASIVE AND NON INVASIVE
STRATEGIES AFTER UNCOMPLICATED MYOCARDIAL INFARCTION IN ELDERLY PATIENTS

TRIAL WORKING PARTY

Principal investigators:

Non invasive strategies : Alessandro Desideri, MD, S.Giacomo Hospital, Castelfranco Veneto

Invasive vs Non invasive:

FE \geq 40%

Salvatore Pirelli , MD,
Niguarda Hospital, Milano

FE <40%

Clara Carpeggiani, MD ,
CNR Institute of Clinical Physiology, Pisa

Monitoring Committee:

Alessandro Desideri, MD, Salvatore Pirelli, MD, Clara Carpeggiani, MD, Paolo Fioretti, MD, PhD, FESC, FACC, Institute of Cardiology, Udine, Eugenio Picano, MD, PhD, FESC, CNR, Institute of Clinical Physiology, Pisa

Data base and Statistical Analysis:

Dario Gregori, MA, PhD, Foundation for Applied Clinical and Basic Research, (IRCAB), Udine

Financial Committee:

Leopoldo Celegon, MD, S.Giacomo Hospital, Castelfranco Veneto

Quality Assesment:

Echocardiography: Eugenio Picano, MD, PhD, FESC ,according to EPIC, EDIC

Coronary angiography : Giambattista Danzi, MD

THE RATIONALE

Risk stratification early after an acute myocardial infarction remains a major goal in clinical decision making. Predischarge clinical evaluation often allows to identify high risk patients during the acute phase of myocardial infarction. In patients with **non complicated myocardial infarction** (i.e. patients without pump dysfunction, severe arrhythmias or early recurrence of ischemic symptoms) different stratification modalities have been proposed. The simple **clinical data** obtained during the acute phase (absence of signs/symptoms of left ventricular failure, pulmonary congestion at chest X-ray etc) often allow to identify a group of patients at very low risk for future events. Noninvasive stress tests have repeatedly proven to have risk stratification capability, and for this good reason they are performed. **Exercise testing** is still the most commonly used method because simple and easily available (1-6) More recently , **stress echocardiography** has gained popularity (7-12), in view of its high accuracy in detecting residual jeopardized myocardium that can be used to assess prognosis. These tests, however, are given limited confidence and their destiny of modern Cassandra of Cardiology is to remain unheard and to witness the proliferation of noninvasive examinations. There is a trend towards the increasing use of **coronary angiography** for patients who survive uncomplicated AMI (13). In USA, in patients < 65 years in the early post-infarction period, in whom 15% of all PTCA' s are performed, only 10% of procedures have an abnormal stress test (14). 71% of the 21772 patients enrolled in the GUSTO trial underwent coronary angiography before hospital discharge and 58% of these were treated with PTCA or bypass surgery . In the field of prognostic stratification, in the absence of carefully conducted studies, the choice between coronary angiography as the only essential study, or use of a non-invasive test to discriminate access to catheterization currently reflects alternative philosophical approaches rather than scientifically based decision (15-16). However, the costs associated with philosophical choice are enormous. Now it is time to address the following issues on the basis of facts rather than opinions:

Issue 1: Is exercise testing still the best non invasive modality for risk stratification, or is stress echo better?

Issue 2: Are non invasive strategies better than invasive ones?

AIM OF THE STUDY

1. Determine a reduction of the costs associated with the management of AMI patients by means of a non invasive strategy that can identify patients at low risk very early , allowing early hospital discharge. This reduction may be considered relevant if the predictive value of this strategy is at least similar to that of conventional strategies and is not accompanied by a higher number of events.
2. Compare two strategies - invasive , non invasive - in risk assesment and cost profile

METHOD AND STATISTICAL DESIGN

The study is designed as a prospective randomized multicenter parallel trial. Several factors have a strong prognostic value in not complicated IMA, like, for instance, sex, age, trombolitic therapy. The latter has an estimated effect of 10-15% in terms of hard events. Age has been considered in the protocol limiting the eligibility of the patients to those older than 75 years. Therefore, assuming a non-homogenous (among centers) non-compliance of 5% and a minimal relative difference in terms of costs of 15% among strategies, the sample size needed to get a power of .80 at an alpha level of 0.05 is equal to 753 patients for each group of patients.

INCLUSION CRITERIA

All patients being admitted to the partecipating centers with a diagnosis of non complicated myocardial infarction, with beginning of the symptoms less than 24 hours, giving informed consent.

The diagnosis of acute myocardial infarction rests on the following criteria: typical pain and/or appearance of pathological q waves and/or evolving modifications of ST/T segment at ecg, in the presence of a raise of CPK and CK-MB.

The absence of complications is defined by the absence of clinical and/or radiographic signs of left ventricular failure, absence of major arrhythmias or recurrent angina and presence of an echocardiographic examination performed on Day 3 demonstrating $EF \geq 40\%$

EXCLUSION CRITERIA

Age >75

Episode of ventricular fibrillation

Atrio-ventricular blocks

Left bundle brunch block

Pericarditis

Insufficient echocardiographic window (acceptable window : ≥ 13 segments adequately visualized in at least 1 projection)

Patients with a short-term prognosis (e.g.cancer)

Patients refusal to take part to the study. The data of these patients will have to be collected anyway.

The Centers taking part to the trial will be assigned to one of the following randomizations:

Group I. Strategy 1 (“echocentric”) vs Strategy 2 (“ergocentric”)

that will compare the predictive value of stress echo and exercise testing

Group II Strategy 3 (“echocentric” with early discharge) vs Strategy 4 (“clinical”)

that will determine the reduction of costs determined by Strategy 3 (stress echo)

Group III Strategy 5 (“non invasive”) (echo or exercise testing according to EF) vs Strategy 6 (“invasive”)

PHARMACOLOGICAL STRESS- ECHOCARDIOGRAPHY

The stress echo of first choice is dipyridamole stress echo; dobutamine stress echo will be performed when dipyridamole is either contraindicated or non diagnostic at submaximal dose load.

Patients are instructed so as to avoid drinking coffee, tea or cola within 8 hours before the tests.

Dipyridamole Two dimensional echocardiography will be performed in Day 3 -5 , in therapy, at rest and in combination with dipyridamole infusion (0.56 mg/kg over 4 minutes followed by 4 minutes of no dose and if negative , by a second dose of 0.28 mg/kg in 2 minutes , with a cumulative dose of 0.84 mg/kg over n 10 minutes). The test will be interrupted by aminophilline at 15th minute for the negative tests or when a clear asynergy will appear (70-240 mg in 1 to 3 minutes). All standard projections will be recordered at rest.

In patients in whom dipyridamole test is contraindicated (for concomitant xanthine therapy or severe bronchopneumopathic disease , or in those with submaximal dipyridamole test (for limiting side effects at the low dose) dobutamine test will be performed.

Dobutamine Dobutamine is infused in 3 minutes dose increments, starting from 5 mcg/kg per minute and increased to 10, 20, 30 and 40 mcg/kg per minute. Infusion is immediately stopped as soon as criteria for positivity are reached during the test.

Diagnostic end points. Positivity of the test is based on the detection of a transient ventricular dyssynergy of contraction, which was absent or of a lesser degree in the baseline examination. Diagnostic end points, apart development of dyssynergy of contraction, are: peak drug dose; achievement of conventional non-echocardiographic "ischemic " end-points (sever chest pain and/or ST segment shift >2 mV). The test is also stopped, in the absence of diagnostic end-points, for one of the following reasons: 1) intolerable symptoms; 2) limiting asymptomatic side effects, consisting of hypertension (systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg), hypotension (30 mmHg decrease in blood pressure), severe supraventricular or ventricular arrhythmias.

Echocardiographic analysis . Two-dimensional echocardiographic monitoring is performed throughout and up to 5 minutes after the stop of drug infusion. The left ventricular wall will be divided in 16 segments;segmental wall motion will be graded as follows: 1=normal, 2=hypokinetic, 3= akinetic, 4=dyskinetic. Wall motion score index and ejection fraction at rest as well as wall motion score index at peak stress will be calculated, by the summation of individual segment score divided by the number of segment interpreted. A test result will be considered positive when the wall motion score will increase by one or more in two or more adjacent segments as compared to rest . An akinesis becoming diskinesis will not be considered a positive test. The ejection fraction will be calculated on a single plane according to the area-length method.

At each Center, one reader who had passed the quality control procedures adopted for EPIC protocol will review the study; his or her reading will be entered directly into the data bank

EXERCISE TESTING

The patients assigned to the ergocentric strategy will perform a maximal symptom limited exercise testing, in full therapy. The test will be performed on day 7-9 in Group I, and on day 5-6 in Group III. The

initial work load will be 25 W, with 25 W increments every 2 minutes. In the case of treadmill, Bruce protocol will be adopted . Criteria for stopping the test will be: fatigue, triplets of ventricular premature beats, hypotension, excessive rise of blood pressure, ST segment depression >3 mm, worsening angina, ST segment depression and angina at low workload.

ST segment depression >1 mm is defined as positive exercise testing.

The patient that will not be able to perform the exercise testing (for vascular or orthopedic problems) will be assigned to stress echo evaluation as previously described.

CLINICAL EVALUATION

The clinical evaluation will include chest X ray at hospital admission, two dimensional echocardiography without stress on Day 3 and clinical evaluation and electrocardiogram every day.

CORONARY ANGIOGRAPHY

Left sided heart catheterization and selective right and left coronary angiography are performed in standard manner using either Judkins or Sones technique. Angiograms are reviewed by two angiographers . Significant coronary stenoses are defined as >70% reduction in the luminal diameter of any of the main coronary arteries or >50% reduction of the luminal diameter of the left main coronary artery. Coronary revascularization by angioplasty and/or coronary artery bypass surgery will be performed when anatomically indicated.

Recommended treatment will be revascularization of the infarct vessel, whenever possible, if ejection fraction will be superior 40%.In case of an ejection fraction <40% recommended treatment will be complete revascularization (with PTCA or CABG)

FOLLOW UP

Primary endpoints:

The following events will be considered:

Hard events: death, non fatal myocardial infarction

Soft events: unstable angina followed by hospital admission, revascularization procedures (PTCA or aorto-coronary bypass graft)

With the only exception being the case of death of the patient, in all other cases the follow up will last 1 year.

Secondary endpoints:

Frequency and duration of hospital admission due to any cause

Frequency and costs of the various diagnostic and therapeutic procedures

Quality of life evaluation (16)

A questionnaire for quality of life will be given to all patients at 2-4 weeks, 6 and 12 months follow up

STUDY DESIGN

NON INVASIVE STRATEGIES

Group I Randomization on Day 3 (after Chest X ray and rest Echo)

Echocardiogram: Ejection Fraction $\geq 40\%$

Strategy 1 Stress echo under therapy (Day 3-5)

Strategy 2 Maximal symptom limited exercise testing under therapy (Day 7/9)

All patients will be discharged in Day 7-9

Group II Randomization in day 3 (after Chest X ray and rest echo)

Echocardiogram: EF $\geq 40\%$

Strategy 3 Stress echo (under therapy) in Day 3-5 and hospital discharge in Day 4-6 if negative stress echo.

Strategy 4 Clinical evaluation and hospital discharge in Day 7-9

All patients (Strategy 1-2-3-4) will perform a maximal symptom limited exercise testing under therapy at 2-4 weeks.

INVASIVE VS NON INVASIVE STRATEGY

Group III Randomization in day 3 (after Chest X ray and rest echo)

If EF \geq 40%, then randomization to

Strategy 5 ** Maximal symptom limited exercise testing (under therapy)** (Day 5-6)

If positive <6 minutes then coronary angiography

If positive between 6-8 minutes, then stress echo

If positive >8 minutes, follow up, like negative tests

vs

Strategy 6 **Coronary angiography**

and revascularization of the infarct vessel

If EF <40%, then randomization

Strategy 5 *Stress-echo**

If positive, then coronary angiography

If negative, follow up

vs

Strategy 6 ** Coronary angiography**

and complete revascularization (PTCA or CABG)

Follow up will be of 12 months. The patients will be followed in the outpatient clinic at 2-4 weeks, at 6 and 12 months.

PATIENTS EXCLUDED FOR REFUSAL TO TAKE PART IN THE STUDY

The refusal to take part in the study is a confounding factor that reduce the efficiency of the study (17). The data of these patients will be collected for a preliminary study that should confirm the existence or on the contrary quantify the bias due to selection. Also the data of the patient not included in the study for one of the exclusion criteria will have to be collected.

BIBLIOGRAFY

1. De Busk RF, Blomqvist CG, Koughoukos NT Identification and treatment of low risk patients after acute myocardial infarction and coronary artery bypass graft surgery *N Engl J Med* 1986; 314:161-166
2. Starling M R, Crawford M H, Kennedy G T et al Exercise testing after myocardial infarction: predictive value for subsequent unstable angina and death *Am J Cardiol* 1980;46:909-914
3. Theroux P, Waters D, Halphen C et al Prognostic value of exercise testing soon after myocardial infarction *N Engl J Med* 1979;301:341-345
4. Epstein SE, Palmieri ST, Patterson RE Evaluation of patients after acute myocardial infarction: indications for cardiac catheterization and surgical interventions *N Engl J Med* 1982; 307:1482-1487
5. Campbell S, A'Hern R, Quigley P et al Identification of patients at low risk of dying after acute myocardial infarction by simple clinical and submaximal exercise test criteria *Eur Heart J* 1988;9, 938-947
6. Velasco J, Tormo V, Ferrer LM et al Early exercise test for evaluation of long term prognosis after uncomplicated myocardial infarction *Eur Heart J* 1981;2:401-407
- 7 Picano E, Landi P, Bolognese L et al Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: a large scale, multicenter trial *Am J Med*; 95 (6):608-618
- 8 Camerieri A, Picano E, Landi P Prognostic value of dipyridamole echocardiography early after myocardial infarction in the elderly patients *J Am Coll Cardiol* 1993; 22(7):1809-1815
- 9 Sclavo MG, Noussan P, Pallisco O, Presbitero P Usefulness of dipyridamole-echocardiographic test to identify jeopardized myocardium after thrombolysis *Eur Heart J* 1992;13:1348-1355
10. Chiarella F, Domenicucci S, Bellotti P Dipyridamole echocardiographic test performed 3 days after an acute myocardial infarction: feasibility, tolerability and in-hospital prognostic value
Eur Heart J, 15(6) 842-850,1994
- 11 Picano E, Pingitore A, Sicari R et al Stress echocardiographic results predict risk of reinfarction early after uncomplicated acute myocardial infarction: large scale multicenter study *J Am Coll Cardiol* 1995;26:908-913
- 12 Van Daele M, Mc Neil A, Fioretti P et al Prognostic value of dipyridamole sestamibi single-photon emission computed tomography and dipyridamole stress echocardiography for new cardiac events after an uncomplicated myocardial infarction *J Am Soc Echocardiogr* 1994, 7(4) 370-380
- 13 Verani MS Should all patients undergo cardiac catheterization after a myocardial infarction? *J Nucl Cardiol* 1994; 1: S 134-146
- 14 Topol EJ, Ellis SG, Cosgrove DM et al, Analysis of coronary angioplasty practice with an insurance-claims data base. *Circulation* 1993; 87:1489-1497

15 Bodenheimer MM Risk stratification in coronary disease: a contrary viewpoint. *Ann Int Med* 1992; 116:927-936

16 Lim L, Valenti L, Knapp J et alii A self administered quality of life questionnaire after acute myocardial infarction *J Clin Epidemiol* 1993; 46, 1249-1256

17 Gorkin L, Schron E, Handshaw K et alii Clinical trials enrollers vs nonenrollers: the Cardiac Arrhythmia Suppression trial (CAST) Recruitment and Enrollment Assesment in Clinical trials (REACT) project *Control Clin Trials* 1996; 17(1):46-59