ANMCO Research Center

STORY

ANMCO is the Italian Association of Hospital Cardiologists, a no-profit professional association of over 5000 Italian Cardiologists operating within the National Health Service. Founded in 1963, ANMCO is dedicated to promote optimal care, prevention and rehabilitation of cardiovascular diseases through organization’s proposals, clinical research, professional education and CME programs.

It also has a key role in the development and implementation of standards and guidelines for cardiological clinical practice in Italy.

In 1992 ANMCO created the ANMCO Research Center, responsible for planning and conducting the scientific and cultural projects of the Association.

In 1998 ANMCO founded the Heart Care Foundation, legally recognized by the Ministry of Health on September 2000. Heart Care Foundation is registered in the ONLUS registry.

The aim of the foundation was to provide citizens with a correct information on cardiovascular diseases and to support scientific research in the cardiovascular field. ANMCO Research Center activities passed therefore to HCF.

TEAM

Director

Aldo P. Maggioni

Data Managers

Marco Gorini
Giampietro Orsini
Daniela Viva
Daniele Dall’Osso

Statisticians

Donata Lucci
Lucio Gonzini

Statisticians

Donata Lucci
Lucio Gonzini

Regulatory and Administration

Andrea Lorimer
Paola Priami
Laura Costanzo

the ANMCO Research Center staff

Medical Consultants

Gianna Fabbri
Samuele Baldasseroni
Rinaldo Lavecchia
Angela Franchi
Francesco Orso

Assistants

Barbara Bartolomei
Laura Sarti
Ilaria Cangioli
Elisa Bianchini
Laura Cipressa
Tiziana Benassai

Monitoring

Martina Ceseri
Francesca Bianchini
Arianna Tafi
Iacopo Cangioli
Giuseppe Lonardo

17 external clinical monitors

NETWORK

The ANMCO Research Center clinical Network consists of:

5147 Cardiologists
643 GPs
872 Cardiology Centers
80 Internal Medicine Divisions

This large network of cardiology centers, involved in co-operative activities, offers the possibility to conduct large observational or controlled studies enrolling patients of real world clinical practice where they are routinely treated. In this way, research and clinical practice finish to coincide, offering an incredible opportunity to optimize the quality of patient care.

Such a big network gives also the possibility to translate the research results directly to clinical practice narrowing the gap between scientific knowledge and patient care.
ACTIVITIES

- Evaluation of clinical epidemiology of cardiovascular disease in Italy
- Use of resources and evaluation of their appropriateness
- Diagnostic and therapeutic approaches for major cardiovascular diseases
- Management of clinical trials and outcome research studies

The Staff, the clinical network and the long term expertise in the cardiology field give ANMCO Research Center the possibility to manage each aspect of a clinical trial such as:

- Planning and preparing study protocols
- Managing regulatory and administrative aspects of clinical trials
- Safety surveillance
- Medical communication (study material, newsletter, etc.)
- Clinical monitoring
- Clinical helpline
- Clinical events adjudication
- Data management
- Statistical analysis
- Publications

The ANMCO Research Center possesses all the tools required to manage clinical studies focused on crucial clinical questions that can lead to results with a significant impact on the clinical practice.

The conduction of the research is continuously monitored by a group of clinical monitors trained in-house and co-ordinated by ANMCO Research Center. The group has a central function: it is the guarantee of a careful and appropriate management of the trial and assists and helps researchers in the management of study procedures, as established by the Good Clinical Practice rules.

COLLABORATION

ANMCO Research Center collaborates with independent institutions such as US National Institute of Health, the Italian Ministry of Health or the European Society of Cardiology, fully managing a study or just co-ordinating the Italian Network.

Due to the consolidated network of cardiology centers and the expertise in managing research activities, the ANMCO Research Center has also co-ordinate the Italian component of multinational large-scale clinical trials planned by pharmaceutical companies.

GISSI Studies
ANMCO together with the “Mario Negri” Institute for Pharmacological Research is the promoter of the GISSI Studies since the very beginning. In this context the ANMCO Research Center is serving as Coordinating Center for two current GISSI projects (GISSI Heart Failure and GISSI Atrial Fibrillation).

The identification of real clinical problems, the organization of studies aimed to clarify or solve some of these problems, the network of the centers, well representing real clinical practice, the expertise of the staff in managing trials, the full independence in conducting and interpreting results, the quick transferability of the study results to clinical practice contributed to plan and implement appropriate health policies for the management of cardiovascular diseases.
**PROJECT REVIEW**

The ANMCO working groups or any member of the Association can propose a project of research. Each proposed research project is evaluated by a scientific committee nominated by the ANMCO board, which provides an expert opinion about the scientific plausibility of the study. Then, the Research Center verifies the feasibility of the proposal, defines the costs and guarantees the technical and scientific accuracy of study management.

A pharmaceutical or device company can support the approved projects of research. In any case, the property of the database and the right to publish the results remain by contract in the hands of the Foundation, assuring the full independence of the projects.

The ANMCO Research Center has the full responsibility of the conduct of most of the studies approved by the ANMCO board.

**SELECTED REFERENCES OF YEAR 2004**


The Story by Luigi Tavazzi

After having oriented the co-operative Italian clinical research on acute myocardial infarction for ten years with the GISSI 1, 2, 3, in 1995 we decided to focus the attention of clinical research on the problem of heart failure as well, but with different objectives and methods. The aim was to make a systematic analysis of the universe of patients with heart failure seen by cardiologists, the methodology was observational research.

Through the Research Center, which was then taking on a professional organization, ANMCO conducted its ‘flash’ studies, of extremely short duration (enrolment over two weeks) but extended throughout the country: the SEOSI, which included 3921 patients from both cardiology hospital wards and outpatient clinics, and EARISA, which included 6030 in-patients of whom 1089 had heart failure. In addition, IN-CHF, a registry of outpatients, was established.

Other studies on the outcome of heart failure followed. A large, randomized intervention study, GISSI-HF, is underway and a survey on acute heart failure has just been completed. Thus, IN-CHF is set in the context of the Italian cardiology community’s continuing interest in the huge epidemiological field of heart failure, explored using different and complementary methods.

IN-CHF is approaching its 10th anniversary, after having enrolled about 25,000 patients through approximately 200 cardiology centers. Besides offering a detailed picture of the national clinical activity concerning outpatients with heart failure seen from the hospital point of view, this registry has represented an important conversion for us to meet and has been a collective experience for all of us, one of the instruments through which a group of doctors becomes a scientific community.

As for all voluntary initiatives, it has its limits (consecutiveness of the patients, some inaccuracy and less than perfect continuity of data collection); nevertheless, given that it offers no reward other than knowledge, it is extraordinary that it has survived.

It must, however, be remembered that time erodes: tiredness, hospital life that has become more demanding and stressful, and some frustration about scientific consequences judged by some not to have occurred. The natural history of heart failure, typically oscillating between periods of stability and instability, leads the patients from outpatient clinics into hospital and vice versa. A database collecting information on these different disease courses must be flexible in order to be able to follow them. The Heart Failure Area of the ANMCO is evaluating this important conversion of IN-CHF into an instrument for complete follow-up. I hope that this conversion takes place in order to ensure other decades of life to the already time-honored IN-CHF.

### ANALYSIS ON 21909 PATIENTS

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n (%)</th>
<th>Mean±SD (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td></td>
<td>12679 (57.87%)</td>
</tr>
<tr>
<td>≥70</td>
<td></td>
<td>9230 (42.13%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>15590 (71.16%)</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>6319 (28.84%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td></td>
<td>16131 (73.63%)</td>
</tr>
<tr>
<td>III-IV</td>
<td></td>
<td>5778 (26.37%)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td></td>
<td>19407 (88.55%)</td>
</tr>
<tr>
<td>≥100</td>
<td></td>
<td>2141 (9.27%)</td>
</tr>
<tr>
<td>not available</td>
<td></td>
<td>367 (1.68%)</td>
</tr>
<tr>
<td>EF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td></td>
<td>4264 (19.46%)</td>
</tr>
<tr>
<td>30-40</td>
<td></td>
<td>5786 (26.41%)</td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td>3884 (17.73%)</td>
</tr>
<tr>
<td>not available</td>
<td></td>
<td>7975 (36.40%)</td>
</tr>
<tr>
<td>Cardio-thoracic ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.55</td>
<td></td>
<td>543 (2.48%)</td>
</tr>
<tr>
<td>&gt;0.55</td>
<td></td>
<td>795 (3.63%)</td>
</tr>
<tr>
<td>not available</td>
<td></td>
<td>20571 (93.89%)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td></td>
<td>708 (3.23%)</td>
</tr>
<tr>
<td>100-130</td>
<td></td>
<td>11726 (53.52%)</td>
</tr>
<tr>
<td>&gt;130</td>
<td></td>
<td>9475 (43.25%)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td>8520 (38.89%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>3442 (15.71%)</td>
</tr>
<tr>
<td>DCM</td>
<td></td>
<td>6443 (29.41%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1304 (5.99%)</td>
</tr>
<tr>
<td>EF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td></td>
<td>4264 (19.46%)</td>
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<tr>
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<td></td>
<td>6443 (29.41%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1304 (5.99%)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.5</td>
<td></td>
<td>11237 (51.29%)</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td></td>
<td>416 (1.90%)</td>
</tr>
<tr>
<td>not available</td>
<td></td>
<td>10256 (46.81%)</td>
</tr>
</tbody>
</table>
A large scale clinical trial testing the effects of n-3 PUFA and Rosuvastatin on mortality/morbidity of patients with symptomatic Congestive Heart Failure

**Steering Committee:** L. Tavazzi (Chairman), G. Tognoni (Co-Chairman) M.G. Franzosi, R. Latini, A.P. Maggioni, R. Marchioli, G.L. Nicolis, M. Porcu

**STUDY PARTIALLY SUPPORTED BY PFIZER, SPA, SIGMA TAU FOR THE N-3 PUFA HYPOTHESIS AND BY ASTRAZENECA FOR THE STATIN HYPOTHESIS**

**BACKGROUND**
While pharmacological treatments specifically targeted to the cardio-circulatory system have been largely investigated, scanty controlled data are available concerning the role of dietary and metabolic approaches in the management/outcome of patients with heart failure. A large scale, randomized, clinical trial is proposed to test the effects of (a) n-3 PUFA and (b) a lipid lowering agent on top of the best recommended treatments for heart failure.

**STUDY DESIGN**
The GISSI-HF is a prospective, multicenter, randomized, double blind, placebo controlled study, with randomized allocation of patients with a clinical diagnosis of heart failure to:

- Randomization 1 (R1): n-3 PUFA 1 g daily vs corresponding placebo;
- Randomization 2 (R2): rosuvastatin 10 mg daily vs corresponding placebo.

**OBJECTIVES OF THE STUDY**

**PRIMARY OBJECTIVES**
- All-cause mortality
- All-cause mortality or hospitalizations for cardiovascular reasons

**OTHER END-POINT MEASURES OF EFFICACY**
- Cardiovascular mortality
- Cardiovascular mortality or hospitalizations for heart failure or for any reason
- Sudden cardiac death
- Hospitalizations for any reason
- Hospitalizations for cardiovascular reasons
- Hospitalizations for congestive heart failure
- Myocardial infarction
- Stroke

**FINAL TOP TEN**

<table>
<thead>
<tr>
<th>Center</th>
<th>N° of pts. enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUGANO (CH)</td>
<td>142</td>
</tr>
<tr>
<td>CARDIOCENTRO TICINO SRC</td>
<td>136</td>
</tr>
<tr>
<td>CORTONA (AR)</td>
<td>115</td>
</tr>
<tr>
<td>SPEZIALE INFERMI S. MARIA MISERICORDIA</td>
<td>115</td>
</tr>
<tr>
<td>BONIFACIO (VR)</td>
<td>106</td>
</tr>
<tr>
<td>OSPEDALE CIVILE</td>
<td></td>
</tr>
<tr>
<td>ASCOLI PICENO (AP)</td>
<td></td>
</tr>
<tr>
<td>OSPEDALE G. LE PROVILE C.G. MAZZONI</td>
<td>106</td>
</tr>
<tr>
<td>TERNI (TR)</td>
<td></td>
</tr>
<tr>
<td>AZIENDA USL 4 TERNI</td>
<td></td>
</tr>
<tr>
<td>S. FELICE A CANCELLO (CE)</td>
<td></td>
</tr>
<tr>
<td>OSPEDALE AVE GRATIA PLENA</td>
<td>89</td>
</tr>
<tr>
<td>PAVIA (PV) - IRCCS</td>
<td>88</td>
</tr>
<tr>
<td>FONDAZIONE SALVATORE MAUGERI</td>
<td>88</td>
</tr>
<tr>
<td>CASARANO (LE)</td>
<td>86</td>
</tr>
<tr>
<td>PRESIDIO OSPEDALIERO F. FERRARI</td>
<td>86</td>
</tr>
<tr>
<td>PASSINARA-RIO (MI)</td>
<td>83</td>
</tr>
<tr>
<td>OSPEDALE CIVILE</td>
<td></td>
</tr>
<tr>
<td>ALBANO LAZALE (RM)</td>
<td>82</td>
</tr>
</tbody>
</table>

**EXCLUSION CRITERIA FOR R2 (statin hypothesis):**
- current serum creatinine level >2.5 mg/dL;
- current ALT, AST level >1.5 times the upper normal limit;
- current CPK upper normal limits.

**NUMBER OF PATIENTS TO BE RECRUITED**
Since the trial is event driven, the number of expected deaths which are needed to allow a reliable evaluation of the efficacy of tested drugs is set for both R1 and R2 at 1252 for a study power of 90% at the significance level α=0.045.

**STUDY ADVANCEMENT**
Randomization closed on February 28, 2005, reaching the targeted number of patients. The follow-up period will continue until the number of 1252 fatal events will be accumulated. The expectation is that study results will be available by the end of year 2007.
AREA IN-CHF

AntiRemodeling Effect of Aldosterone Receptors Blockade with Canrenone IN Chronic Mild Heart Failure

Working Group: Heart Failure
Steering Committee: A. Boccanelli (Chairman), G. Cacciatore, F. Clemenza, G. De Simone, A. Di Lenarda, A. Gavazzi, G.F. Mureddu, M. Porcu

STUDY PARTIALLY SUPPORTED BY GIENNE PHARMA

RATIONALE

RALES study has shown that spironolactone reduces the risk of morbidity and mortality, in patients with mild heart failure reducing both progression of heart failure and sudden death. Spironolactone may be effective because it opposes the effects of aldosterone on sodium retention, loss of magnesium and potassium, sympathetic activation, baroreceptor function, vascular compliance and cardiac fibrosis.

In a substudy of RALES trial baseline serum PIIINP, a marker of cardiac fibrosis synthesis, showed an independent negative correlation with survival and CHF hospitalization in the placebo group.

Inhibition of myocardial fibrosis by aldosterone receptor blocker may be particularly useful in the early stages of the disease to reduce ventricular remodeling and to prevent the development of overt heart failure.

STUDY OBJECTIVES

To evaluate the change of left ventricular volumes, ejection fraction and diastolic function induced by treatment with canrenone for twelve months in patients with mild heart failure assuming standard therapy.

The project has also the aim of evaluating the neurohumoral profile including plasma aldosterone level, BNP and PIIINP.

STUDY DESIGN

Multicentric, randomized, double blind, parallel group comparison of canrenone 25-50 mg od vs placebo.

500 patients with HF, NYHA II, EF ≤45%, aged 18-80 years, on stable recommended therapy will be enrolled by 50 centers.

Follow up visits and laboratory examinations are performed monthly for the first three months, then every three months up to the end of the study (12 months).

STUDY ADVANCEMENT (as of May 13, 2005)

1. Enrollment period: July 2002 - June 2005
2. Activated Centers: 46
3. Enrolled patients: 476
4. Top Five: (as of May 13, 2005)
   - Ospedale Tiarini Corticella - Bologna 32 pts
   - Ospedale Civile - S. Bonifacio (VR) 31 pts
   - Ospedale Civile - Passirana Rho (MI) 27 pts
   - Ospedale S. Giovanni - Roma 24 pts
   - Fondazione San Raffaele G. Giglio - Cefalù (PA) 22 pts

Baseline characteristics (Forms entered as of April 30, 2005)

| Patients | 440 |
| Centers | 46 |
| Males | 82.5% |
| Age (mean±SD) | 62±9 |
| History of hypertension | 46.4% |
| Diabetes | 21.4% |
| PVD | 5.7% |
| COPD | 13.9% |
| Ictus | 3.2% |
| At least one hospitalization for HF | 48.6% |
| HF diagnosed from | |
| < 6 months | 8.9% |
| 6-18 months | 24.1% |
| 19-48 months | 29.1% |
| > 48 months | 37.9% |
| Etiology | |
| Ischemic | 53.4% |
| Dilatative | 30.2% |
| Hypertensive | 10.0% |
| Other | 6.4% |
| Ejection fraction | |
| < 30% | 17.4% |
| 30-40% | 64.1% |
| > 40% | 18.5% |
Survey on Acute Heart Failure

Working Group: Heart Failure

Steering Committee: L. Tavazzi (Chairman), G. Cacciatore (Co-Chairman), G. Ansalone, F. Oliva, M. Porcu

STUDY PARTIALLY SUPPORTED BY ABBOTT ITALY

RATIONAL

The combination of the ageing of the population and the improvement in survival after acute myocardial infarction has created a rapid growing in the number of patients currently living with chronic heart failure and this trend is likely to continue for the near future. With the increased prevalence of heart failure there is a concomitant increase in the number of related hospitalizations and it is important to recognize that as heart failure progresses the risk of acute exacerbations increases.

Acute heart failure is characterised by acute onset of symptoms such as shortness of breath and by haemodynamic abnormalities and neuroendocrine activation. This can occur either de-novo or as acute exacerbation of chronic heart failure.

Compared with the dramatic development of novel therapies in the last 30 years for patients with other cardiovascular diseases, or with chronic heart failure the options available to treat acute heart failure are limited. Current guidelines suggest that the available treatment modalities are bed rest, morphine, oxygen, diuretics, vasodilators, inotropic agents, with and without vasodilating effects. These therapeutic measures aim to relieve symptoms, improve haemodynamic abnormalities and reduce morbidity and mortality.

While several data from registries and surveys describing the diagnostic and therapeutic approaches adopted in clinical practice in patients with chronic heart failure are available in the literature, scarce data have been collected in patients with acute heart failure.

OBJECTIVES

The main objective of the study is to describe an updated clinical epidemiology of the patients with acute heart failure admitted to a cardiology department provided with an Intensive Cardiology Care Unit.

Secondary Objectives are:
- To identify diagnostic and therapeutic approaches to manage acute heart failure
- To assess in hospital patients’ outcome and its prognostic predictors
- To describe the routine practice of the involved centers in following patients within the six months after hospital discharge

STUDY DESIGN

National, multicentric, prospective, observational study.

All the existing Italian departments with an Intensive Cardiology Care Units were invited to participate to the study.

Data were collected over 3 months in all eligible patients admitted in the participating clinical cardiology centers at the time of hospital admission.

Data on availability of follow up information were collected for each patient 6 months after discharge. Investigators entered directly the clinical data on an electronic CRF, through a Web based system.

STUDY POPULATION

All consecutive patients admitted with a primary diagnosis of acute new onset heart failure or deterioration of chronic heart failure were screened.

Inclusion criteria:
- All age and both sexes
- Any etiology of acute HF
- NYHA III-IV of new occurrence or deterioration in chronic patients
- Killip 3-4 if heart failure was due to an acute coronary syndrome
- Pulmonary edema or cardiogenic shock
- Need of drug infusion therapy
- Any level of ejection fraction

Being the study observational, all included patients have been treated according to the clinical judgement of the attending cardiologists. Participating centers were invited to follow the suggestions of the most recent guidelines.

<table>
<thead>
<tr>
<th>REGISTRY POPULATION</th>
<th>(2807 patients)</th>
</tr>
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<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>73±11</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1283 45.7</td>
</tr>
<tr>
<td>Female sex</td>
<td>1159 39.5</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
</tr>
<tr>
<td>- none</td>
<td>194 6.9</td>
</tr>
<tr>
<td>- primary schools</td>
<td>1859 66.2</td>
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<tr>
<td>- secondary schools</td>
<td>305 10.9</td>
</tr>
<tr>
<td>- degree</td>
<td>82 2.9</td>
</tr>
<tr>
<td>- unknown</td>
<td>367 13.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IN-HOSPITAL IV TREATMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>Nitroprusside</td>
</tr>
<tr>
<td>Isotropes</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Dobutamine</td>
</tr>
<tr>
<td>Enoximodide</td>
</tr>
<tr>
<td>Levosimendine</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td>Noradrenaline</td>
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<table>
<thead>
<tr>
<th>IN-HOSPITAL USE OF DIURETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Furosemide</td>
</tr>
<tr>
<td>IV furosemide</td>
</tr>
<tr>
<td>Oral furosemide</td>
</tr>
<tr>
<td>Other diuretics</td>
</tr>
<tr>
<td>IV diuretics</td>
</tr>
<tr>
<td>oral diuretics</td>
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</table>

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
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<tbody>
<tr>
<td>54.8% Worsening CHF</td>
</tr>
<tr>
<td>44.0% De Novo HF</td>
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</tbody>
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<table>
<thead>
<tr>
<th>6 MONTH FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1406 (54.1%) clinical follow-up</td>
</tr>
<tr>
<td>1192 (45.9%) no clinical follow-up</td>
</tr>
</tbody>
</table>

*At least 1 visit from discharge to 6 months
PEACE

Prevention of Events with Angiotensin Converting Enzyme inhibition

Steering Committee: Chairman: E. Braunwald, M. Pfeffer  National Coordinator: A.P. Maggioni

STUDY SUPPORTED BY THE NATIONAL HEART, LUNG AND BLOOD INSTITUTE, USA

In collaboration with the George Washington University, USA

OBJECTIVE

To determine whether the addition of an angiotensin converting enzyme (ACE) inhibitor to standard therapy in patients with known coronary artery disease and preserved left ventricular function will reduce the risk of cardiovascular mortality, myocardial infarction, CABG or PTCA.

8290 PEACE participants

Pls and Coordinators at 187 clinical centers

United States  118 clinics  n = 4817 (incl. Puerto Rico)
Canada          32 clinics  n = 2513
Italy           37 clinics  n =  960

INCLUSION CRITERIA

• Age ≥50 years
• Coronary artery disease - MI, or - CABG or PCI, or - Coronary angiogram with obstruction of ≥50% luminal diameter in at least one native vessel
• LVEF >40%
• Tolerated 2 week run-in of 2 mg/day trandolapril

PEACE was conducted in a population with CAD and preserved LV function who received intensive contemporary management. This usually included coronary revascularization and lipid lowering. Consequently, their CV event rate was lower than in HOPE and EUROPA. In this population, the addition of an ACE inhibitor did not reduce further clinical atherosclerotic events.

STUDY CONCLUSION

In low risk patients with stable CHD and preserved LV function who are receiving optimized contemporary management, there is no evidence of further benefit from the addition of an ACE-inhibitor for CV death, MI or coronary revascularization.

GISSI-AF
Randomized, prospective, multicenter study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of Atrial Fibrillation recurrence

Steering Committee: M. Disertori (Chairman), R. Latini (Co-Chairman), A.P. Maggioni, P. Delise, G. Di Pasquale, M.G. Franzosi, L. Staszewsky, G. Tognoni

STUDY PARTIALLY SUPPORTED BY NOVARTIS

In collaboration with Mario Negri Institute, Milan

BACKGROUND
The possibility to prevent atrial fibrillation recurrence with antiarrhythmic agents is very limited, owing to the discouraging results obtained with current drugs in many patients. Data from experimental studies suggest that angiotensin II AT1-receptor blockers (ARBs) can influence atrial remodeling, a key factor in atrial fibrillation initiation and maintenance. Moreover, some preliminary clinical data show that ARBs can prevent atrial fibrillation episodes. GISSI-Atrial Fibrillation is a randomized, prospective, parallel group, placebo-controlled, multicenter study designed to test whether ARBs can reduce atrial fibrillation recurrence.

OBJECTIVES AND METHODS
Primary objective of the study is to demonstrate that, in patients with history of recent atrial fibrillation treated with the best recommended therapies, the addition of the ARBs valsartan (titrated up to 320 mg) is superior to placebo in reducing atrial fibrillation recurrence. A substudy will analyse the effect of valsartan on left atrial dimensions and on neurohormones.

ASSESSMENT SCHEDULE

STUDY ADVANCEMENT (as of May 13, 2005)
Participating centres: 151 Activated centers: 56
Recruiting centres: 24 Patients enrolled: 66

STUDY DESIGN

5. Clinically significant valvular etiologies,
6. Thyroid dysfunction,
7. Indication for pacemaker or ICD implant or for an ablative treatment,
8. Planned cardiac surgery, expected to be performed within 3 months,
9. Serum creatinine level above 2.5 mg/dl,
10. Significant liver disease,
11. Pregnant or lactating women or women of childbearing potential who are not protected from pregnancy by an accepted method of contraception,
12. Any condition that in the opinion of the investigator would jeopardize the evaluation of efficacy or safety or be associated with poor adherence to the protocol,
13. Presence of any non-cardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy,
14. Treatment with any investigational agent within 1 month before randomization,
15. Currently decompensated HF.

NUMBER OF PATIENTS TO BE RECRUITED

The GISSI-AF is the largest trial aimed at assessing the role of ARBs in reducing atrial fibrillation recurrence. The sample size has been calculated with the following assumptions: AF recurrence over 1 year of follow-up in the control group was 50%, relative reduction of AF recurrence with valsartan = 17.6% (from 50% to 41.2%), with 90% power and a 2x error of 0.05. A total of 1402 patients (701 in each arm) will be randomized in a 1:1 ratio to receive valsartan or placebo on top of the existing treatments.

OBJECTIVE 1: To demonstrate that, in patients with a history of recent atrial fibrillation treated with the best recommended therapies, the addition of ARBs valsartan (titrated up to 320 mg) is superior to placebo in reducing atrial fibrillation recurrence.

OBJECTIVE 2: To assess the effect of ARBs valsartan on left atrial dimensions and on neurohormones.

CONCLUSION
The GISSI-AF is the largest trial aimed at assessing the role of ARBs in reducing atrial fibrillation recurrence. The sample size has been calculated with the following assumptions: AF recurrence over 1 year of follow-up in the control group was 50%, relative reduction of AF recurrence with valsartan = 17.6% (from 50% to 41.2%), with 90% power and a 2x error of 0.05. A total of 1402 patients (701 in each arm) will be randomized in a 1:1 ratio to receive valsartan or placebo on top of the existing treatments.
Italian Study on the Cardiovascular Effect of Systolic Blood Pressure Control

STUDY OBJECTIVE

Aim of the study is to ascertain whether an intensive therapeutic strategy aimed to achieve a tighter control of systolic BP (for example, < 130 mmHg) will result in a greater reduction in LVH than a usual strategy (systolic BP reduction < 140 mmHg).

STUDY OBJECTIVE

The primary end-point for the comparison between the two groups will be the change in LVH at ECG. Secondary end-points:

1. To compare the 2 groups in the time course of BP changes.

2. To compare the 2 groups in the primary and secondary end-points only in the subjects who achieved the target BP ( < 140 mmHg and < 130 mmHg)

3. To perform the following pre-specified sub-group analyses:

3.1. Absence vs presence of LVH at randomization.

3.2. Age > vs < 70 years at randomization.

3.2. Men vs Women.

4. To compare the 2 groups in the continuous (Cornell voltage) and non continuous (strain, Rohlhilt-Estes) components of the Perugia score.

5. To assess the relation between BP changes and LVH changes in the total sample and in each group.

6. To compare the two groups in the incidence of a composite pool of major cardiovascular events.

7. To assess the distribution of the different treatments at any visit, both in the total population and in specific subgroups (defined by sex, age, etc). Comparisons between different treatments will not be allowed because treatments are not given according to a randomised sequence and therefore an allocation bias would be most likely to occur.

INCLUSION CRITERIA

To be eligible, patients must meet all the following criteria:

1. Written informed consent to the study.

2. Age ≥ 55 years at randomisation. There is no upper age limit.

3. Clinic blood pressure ≥ 150 systolic in 2 visits at distance of 7-14 days, irrespective of diastolic pressure. Duration of treatment before visit 1 must be at least 12 weeks.

4. At least one additional risk factor including the following:


4.2. Total cholesterol ≥ 200 mg/dl, or HDL cholesterol < 40 mg/dl, or LDL cholesterol ≥ 130 mg/dl.

4.3. Family history of cardiovascular disease in male first degree relative ≤ 55 years or female first degree relative ≤ 65 years.

4.4. Previous TIA or stroke.

4.5. Previous coronary artery disease defined by evidence of:

4.5.1. Documented myocardial ischemia by ECG, stress-echocardiography or scintigraphy, or

4.5.2. Angiographic stenosis > 50% in at least 2 major epicardial vessels, or

4.5.3. Prior aorto-coronary by-pass or percutaneous coronary angioplasty, or

4.5.4. Non Q wave myocardial infarction.

4.6. History of peripheral occlusive arterial disease (claudicatio intermittens associated with angiographic or ecographic evidence of > 60% stenosis).

EXCLUSION CRITERIA

1) Diabetes, defined by fasting glucose > 125 mg/dl in 2 samples or ongoing anti-diabetic treatment.

2) Renal failure, defined by a serum creatinine > 2.0 mg/dl.

3) Chronic atrial fibrillation or flutter.

4) Clinically significant hepatic or haematological disorders, alcoholism, drug addiction.

5) Causes precluding ECG interpretation for LVH: complete right or left bundle block, Wolff-Parkinson-White syndrome, previous Q-wave myocardial infarction.

6) Any disease causing reduced life expectancy.

7) Unwilling to participate.

8) Significant valvular heart disease.

TREATMENT

Antihypertensive therapy will be administered in an open fashion and tailored to the single subject according to individual risk profile defined by concomitant risk factors and diseases, in line with current guidelines. Pharmacologic and non pharmacologic treatment of lipid disorders will also be guided by individual risk profile, according to current guidelines. Achievement of adequate BP control may require adjunct of further drugs to those already taken by patients. Thus, treatment will include different combinations of prior drugs (background therapy) and dispensed drugs. In order to well define applicability of results of the present study to the clinical practice, the use of specific antihypertensive drugs which will be dispensed for the purpose of this study will be restricted according to the following list:

- Diuretics: hydrochlorothiazide (in fixed combination with ramipril or telmisartan), furosemide [25 mg].

- Beta-blockers: bisoprolol [10 mg].

- ACE-inhibitors: ramipril (alone [5 and 10 mg] or in fixed combination with hydrochlorothiazide [ramipril 5 mg + hydrochlorothiazide 25 mg]).

- Angiotensin II receptor antagonists: telmisartan [alone [80 mg] or in fixed combination with hydrochlorothiazide [telmisartan 80 mg + hydrochlorothiazide 12.5 mg]).

- Calcium-antagonists: amlodipine [10 mg].

- Centrally acting sympathic inhibiting drugs: clonidine (transdermal) [2 mg].

STUDY ADVANCEMENT (as of May 13, 2005)

Duration of the study: 4 years (2 years for enrollment, 2 years follow-up)

Patients expected: 1750

Study enrollment started on February 2005

Participating Centers 51

Activated Centers 39

Randomizing Centers 14

Screened Patients 88

Enrolled Patients 69
HEART Survey

Hypertrophy at ECG And its Regression during Treatment

Working Group: Prevention

Steering Committee: P. Verdecchia (Chairman), F. Avanzini, G. De Simone, S. Pede, F. Perticone, G. Schillaci, P. Sleight, D. Vanuzzo

Data Manager: G. Paolo Reboldi

STUDY PARTIALLY SUPPORTED BY RECORDATI

In collaboration with the Associazione Umbria Cuore e Ipertensione (AUCI)

CONCLUSIONS

- Regression of LV hypertrophy at ECG was achieved in 41% of patients.
- Lack of regression of LV hypertrophy was associated with a 3.8 times higher risk of serious cardiovascular complications over a relatively short period (2 to 3 years). Indeed, the crude rate of cardiovascular events was 6.34 x 100 patients per year in patients without LV hypertrophy regression, versus only 2.05 in those with LV hypertrophy regression.
- Overall, the degree of BP control in the community was not satisfactory: only 33% of patients showed complete BP normalization (achieved BP <135/85 mmHg).
- The possible mechanisms underlying the incomplete degree of LV hypertrophy regression may be the following:
  - Degree of BP control still far from optimal.
  - Most patients already under drug treatment at the beginning of the study.
- The prognostic value of the serial changes in the strain pattern is more important than that of the serial changes in the ECG voltages.
- The cheap traditional ECG should be re-evaluated in the management of hypertensive patients in order to refine risk stratification and guide therapy.

PRIMARY AIM

The primary aim of the study was to evaluate the prognostic value of regression of ECG LVH in patients with essential hypertension. The subgroups with persistence and regression of ECG LVH were compared in their subsequent rate of CV events.

DESIGN

Cohort observational study. Treatment was tailored to the single patient and there was no administration of experimental drugs. Study duration was 3 years with clinical visits at 3, 6, 12, 24 and 36 months after entry.

STUDY POPULATION

- Age >45 and <85 years
- Caucasian race
- Treated or untreated essential hypertension with clinic SBP 140 and/or DBP 90 mmHg at entry
- ECG LVH, defined by positivity of the Perugia score in the first baseline ECG study.

SECONDARY AIMS

Evaluation of all fatal cardiovascular events and non-cardiovascular events.

RESULTS

Left Ventricular Hypertrophy

Patients with primary end-point

<table>
<thead>
<tr>
<th>Event</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>12</td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>5</td>
</tr>
<tr>
<td>Other CV Death</td>
<td>8</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>9</td>
</tr>
<tr>
<td>Hospitalized Heart Failure</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3</td>
</tr>
<tr>
<td>TIA</td>
<td>6</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>10</td>
</tr>
<tr>
<td>AV Block (pacemaker implant)</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>64</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Regression of LV hypotrophy at ECG was achieved in 41% of patients.
- Lack of regression of LV hypotrophy was associated with a 3.8 times higher risk of serious cardiovascular complications over a relatively short period (2 to 3 years). Indeed, the crude rate of cardiovascular events was 6.34 x 100 patients per year in patients without LV hypotrophy regression, versus only 2.05 in those with LV hypotrophy regression.
- Overall, the degree of BP control in the community was not satisfactory: only 33% of patients showed complete BP normalization (achieved BP <135/85 mmHg).
- The possible mechanisms underlying the incomplete degree of LV hyper- trophy regression may be the following:
  - Degree of BP control still far from optimal.
  - Most patients already under drug treatment at the beginning of the study.
- The prognostic value of the serial changes in the strain pattern is more important than that of the serial changes in the ECG voltages.
- The cheap traditional ECG should be re-evaluated in the management of hypertensive patients in order to refine risk stratification and guide therapy.
BACKGROUND

Despite considerable advance in the understanding of CHD pathogenesis and availability of effective preventive treatments, post-MI patients are still at high risk of CHD events.

Pre-hospital coronary heart disease deaths outnumber intra-hospital ones, suggesting the need of optimising prevention strategies.

The care of post-MI patients is generally managed separately and independently by cardiologists and general practitioners, thus generating further variability in therapeutic strategies.

The SPS study is aimed at involving various health professionals dealing with post-MI preventive strategies in a collaborative effort to evaluate and eventually achieve a better management of CV risk factors. The major challenges are to:

- Set up a collaborative network between hospitals and general practice
- Define the current status of preventive actions in post-MI patients
- Put into practice secondary prevention schemes adapted to the Italian health system and thus contribute to a reduction of the burden of cardiovascular disease

AIMS

To assess current management strategies in post-MI patients.

To optimise post-MI secondary prevention strategies through an improved interaction between cardiologists and general practitioners.

To disseminate available and up to date scientific evidence on coronary heart disease prevention.

To evaluate medium-long-term prognosis of post-MI patients identifying the main predictors of cardiovascular events in a Mediterranean population in order to draw an updated, specific risk-chart.

STUDY DESIGN

National, multicentre, observational, prospective study.

Inclusion criteria: all patients with previous myocardial infarction, irrespective of time of the event.

Follow-up: 3 years, with annual clinical visits.

WORK PLAN

a) Network of Territorial Research Groups (TRG), each composed of a local cardiologist and 10 general practitioners.

b) Each TRG:

- Scheduled meetings to discuss clinical cases and updated evidence on recent developments in CHD prevention,
- Participated to the observational study on secondary prevention strategies after myocardial infarction.

RESULTS

Baseline characteristics (n. 6123)

Prevalence of Risk Factors

Time between the index myocardial infarction and recruitment

Previous cardiovascular events

Comorbidities

Pharmacological Treatments
PROCARDIS
Precocious Coronary Artery Disease
A study to identify inherited causes of heart disease

International Project Steering Committee: H. Watkins (Chairman), G. Assmann, R. Collins, A. Hamsten, G. Tognoni

National Steering Committee: E. Arbustini, M.G. Franzosi, M. Tubaro, B. Tognoni

STUDY SPONSORED BY ASTRAZENECA, SWEDEN

Study endorsed in Italy by GISSI - Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto

BACKGROUND

• Coronary artery disease (CHD) is a multifactorial disease, which involves the complex interaction between a number of environmental and genetic factors, each of which may exert only a modest effect. The presence of a genetic component under the CHD has been revealed by some evidence:
  - the existence of early-onset myocardial infarcts and of coronary events in low risk individuals;
  - a family history of MI as an independent risk factor for the disease;
  - the estimate of the genetic contribution to CHD susceptibility, given by a relative risk of 3.8, suggested by the results of the Swedish Twin Registry study.

• The environmental component of CHD has been carefully investigated, while the understanding of the genetic component is backward. Previous studies of genetic of CHD have used a "candidate gene" approach (association studies). Results are very often controversial due to the complexity of the trait and to the methodological biases of the studies.

• To develop new approaches to diagnosis, prevention and treatment, is crucial to investigate carefully the genetic variants (polymorphisms), influencing CHD susceptibility.

The need to understand the genetic of a complex trait as CHD, the investigation of which has obtained up to now disappointing results, and the recent technological advances, which now make it possible to apply approaches inconceivable a short time ago, have led to design the PROCARDIS study.

OBJECTIVES

The aim of the PROCARDIS study is to identify new susceptibility genes of precocious coronary artery disease through a genome-wide screen applying statistical methods of linkage analysis followed by a family-based association study.

PROCARDIS data collection (Figure 1)

The PROCARDIS research programme aims:

• To identify genetic loci that confer susceptibility to CHD by conducting a genome-wide search in at least 2000 pairs of siblings who have developed CHD at a relatively early age and in other families informative for such studies.

• To map regions of linkage more closely by, intra-family association studies.

• To identify novel genes and genetic variants that confer susceptibility to CHD, using positional clamping, candidate gene and mutational analysis approaches.

• To characterise the function and physiological role of these genes.

• To determine the impact of these genes on CHD susceptibility in the general population.

• To detect quantitative trait loci (QTLs) associated to a variety of intermediate phenotypes (based on assays measurements) through linkage analysis.

STUDY DESIGN

Eligibility criteria

• Eligible families: two patterns of families are "informative" for PROCARDIS:
  - ASPs (Affected Sibling Pairs): families constituted by two or more siblings who have developed CHD before the age of 65, with or without parents;
  - TDT (Transmission Disequilibrium Test) families: families constituted by one individual who has developed CHD before the age of 65 (proband) and both surviving parents, or one surviving parent and at least one unaffected sibling.

METHODS

FIRST PHASE:

• The PROCARDIS Study applies the non-parametric ASP method in a genome-wide screen.

• It will be determined whether any of the large number of markers measured on all of the chromosomes is inherited by affected siblings within families more commonly then would be expected by chance.

• 400 markers with an average spacing of 10 cM and a mean heterozygosity of 78.9% will be used.

• A sample size of 2000-2500 sibs pairs is required to provide 85% power to detect linkage (p<0.05) and then to discover a locus contributing 10%-15% of the total genetic component of the CHD, considering a λs = 3.8.

SECOND PHASE:

• Next step will be the fine mapping of a given region, resulted as potential linkage from the initial genome-screen, by means a combination of linkage and association analysis.

• Additional ASPs analysis will be carried out and a family-based association analysis (TDT) will be performed on the same and others informative families.

• Each region of potential linkage will be subjected to saturation mapping using 30-50 microsatellite markers at approximately 1 cM intervals.

• QTLs analysis:

The goal is to identify chromosomal regions containing susceptibility loci to various continuous traits: BMI, lipoprotein(a) and to major traits involved in the metabolic syndrome, such as: Insulin, Proinsulin, HbA1C, HDL levels, tryglicerides, BMI, systolic and diastolic blood pressure.

PROCARDIS Study is an international collaboration between the University of Oxford, UK, the University of Münster, Germany, the Karolinska Hospital of Stockholm, Sweden, and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto, Italy (GISSI – Endorsed by ANMCO and Mario Negri Institute for Pharmacological Research).

STUDY ADVANCEMENT (May 2005)

The collection of the PROCARDIS samples is now closed and it is shown in figure 1. The table below reports the total number of sample collected according to the different phases of analyses that will be performed:

<table>
<thead>
<tr>
<th>Collection Cohorts (DNA)</th>
<th>Germany</th>
<th>Italy</th>
<th>Sweden</th>
<th>UK</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPs</td>
<td>251</td>
<td>320</td>
<td>334</td>
<td>1773</td>
<td>2678</td>
</tr>
<tr>
<td>MIMI ASPs</td>
<td>135</td>
<td>187</td>
<td>223</td>
<td>549</td>
<td>1094</td>
</tr>
<tr>
<td>TDT Families</td>
<td>58</td>
<td>446</td>
<td>197</td>
<td>540</td>
<td>1241</td>
</tr>
<tr>
<td>CASES</td>
<td>393</td>
<td>534</td>
<td>564</td>
<td>3206</td>
<td>4097</td>
</tr>
<tr>
<td>Controls</td>
<td>318</td>
<td>432</td>
<td>392</td>
<td>-</td>
<td>1142</td>
</tr>
</tbody>
</table>

1. A full genome wide-screen has been completed with genotyping to a very high standard (using state-of-the-art quality control mechanisms in an SME setting) and with leading statistical genetic analytical expertise. A 440 microsatellite marker genome-wide linkage analysis has been conducted on the first 2000 ASPs.

2. The fine mapping (with microsatellites of 2-5 cM) of specific regions emerged from the full genome screen has been performed. The anticipation is that 10 regions of interest need to be covered, with the aim of distinguishing true, rather then false-positive linkage.

3. To assess the impact of the candidate genes on CAD susceptibility at the population level, a collection of unrelated, unaffected controls (to match existing collection of cases from families with multiple affected individuals) is ongoing in each of the four Countries involved in the PROCARDIS study.

GISSI-PROCARDIS - Coordinating Centre (S. Barlera, B. Chiodini, L. Crociati, L. Ferrario, E. Nicolis, C. Specchia) c/o Istituto Mario Negri Via Eritrea, 62 - 20157 Milano
Tel. 02-9014482/443 - Fax 02-33200049
e-mail: procardis@marionegri.it
GOSPEL

GLObal Secondary Prevention strategiEs to Limit event recurrence after myocardial infarction

Working Group: Prevention


STUDY PARTIALLY SUPPORTED BY SPA - SOCIETÀ PRODOTTI ANTIBIOTICI

In collaboration with the Italian Group of Rehabilitation and Prevention in Cardiology (GICR) and Salvatore Maugeri Foundation, Veruno

BACKGROUND AND AIMS

While evidences on the efficacy of several strategies in post infarction secondary prevention are available, the management of post MI patients according to these evidences is still incomplete. The aim of this study is to evaluate over a long-term period of time the applicability and the effectiveness of two different secondary prevention strategies, implemented in a rehabilitation setting: intensive vs usual approach.

The two strategies will be compared in terms of: lifestyle modifications, patients' compliance to recommended treatments, metabolic profile, BP profile, morbidity/mortality (combined outcome measure of cardiovascular mortality, non fatal reinfarction, non fatal stroke, angina requiring hospitalization or urgent revascularization procedures), cost/effectiveness.

STUDY DESIGN

Multicentric, randomized study. All patients followed a standard 3-6 week rehabilitation program. At the end of this period the patients were randomized to one of the two study arms:

- Intensive approach (monthly visits in the first 6 months, followed by a visit every 6 months for the remaining 3 years of follow-up). Physical training sessions and intensive counselling on secondary prevention strategies are planned in the course of each visit.
- Usual approach.

The patients must be followed-up for at least 3 year (minimum 3 - maximum 5) from study inclusion. In order to be compliant with recent prevention large clinical trials, in which the follow-up scheduled by the protocol is longer than 3 years, the Steering Committee extended the follow-up of the study to the end of 2005.

STUDY POPULATION

Patients with a recent AMI (within 3 months from symptom onset) excluding those with severe concomitant illness and those aged >75 yrs.

STUDY OBJECTIVES

1. To test the hypothesis that opening an occluded infarct related artery (IRA) with percutaneous coronary intervention, including stents, 3-28 days after an AMI in asymptomatic patients who are at increased long-term risk (FE<50% or proximal occlusion of a large coronary artery) will reduce a composite endpoint of mortality, recurrent nonfatal MI, and NYHA Class IV over 3 years (average) of follow-up.

2. To compare, for the two treatments groups:
   - The incremental cost-effectiveness of PTCA for patients with an occluded IRA
   - Health related quality of life
   - The individual components of the primary end-point
   - A composite endpoint of death, recurrent MI, Class IV CHF, sustained ventricular arrhythmia, automatic implantable defibrillator placement or stroke.

STUDY ADVANCEMENT

Enrollment period:
December 2000 - December 2002
Participating centers: 78
Enrolled patients: 3241
End of follow-up: December 2005

BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Age (mean±SD) years</th>
<th>58±9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 years</td>
<td>8.4%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>86.3%</td>
</tr>
<tr>
<td>Females</td>
<td>13.7%</td>
</tr>
<tr>
<td>Years of education</td>
<td></td>
</tr>
<tr>
<td>≤5 years</td>
<td>33.1%</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>66.9%</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>57.1%</td>
</tr>
<tr>
<td>Retired</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

OAT

Occluded Artery Trial

Steering Committee: J. Hochman (Chairperson), G. Lamas (Co-chairman)  National Coordinator: P. Marino

STUDY SUPPORTED BY THE NATIONAL HEART, LUNG AND BLOOD INSTITUTE, USA

In collaboration with the New York University School of Medicine, USA

BACKGROUND

The benefits of establishing early coronary reperfusion in acute myocardial infarction (AMI) have now been established.

However, current pharmacologic strategies fail to achieve effective reperfusion in 30% or more patients, and many patients with occluded infarct arteries do not meet current criteria for use of these agents.

Early angioplasty, an effective reperfusion method, is available to only a small proportion of potentially eligible AMI patients.

Hence, a substantial number of AMI patients exceed the time beyond which acute reperfusion therapy provides any documented benefit.

However several lines of experimental and clinical evidence suggest that late coronary reperfusion may lead to clinically significant reductions in mortality and morbidity.

STUDY OBJECTIVES

1. To test the hypothesis that opening an occluded infarct related artery (IRA) with percutaneous coronary intervention, including stents, 3-28 days after an AMI in asymptomatic patients who are at increased long-term risk (FE<50% or proximal occlusion of a large coronary artery) will reduce a composite endpoint of mortality, recurrent nonfatal MI, and NYHA Class IV over 3 years (average) of follow-up.

2. To compare, for the two treatments groups:
   - The incremental cost-effectiveness of PTCA for patients with an occluded IRA
   - Health related quality of life
   - The individual components of the primary end-point
   - A composite endpoint of death, recurrent MI, Class IV CHF, sustained ventricular arrhythmia, automatic implantable defibrillator placement or stroke.

STUDY STATUS (as of December 31, 2004)

Enrollment main study period:
March 2000 -December 2004
Enrolled pts: 1970 (88 in Italy) Italian participating centers:10
**ORIGIN**

**Outcome Reduction with Initial Glargine InterventioN**

**Operational Committee:** S. Yusuf (Chairman), H. Gerstein (Co-Chairman), G. Dagenais, R. Diaz, A.P. Maggioni, J. Probstfield, A. Ramachandran, M. Riddle, L. Ryden

**STUDY SUPPORTED BY AVENTIS PHARMACEUTICALS**

**OBJECTIVES**

- To determine whether insulin glargine-mediated normoglycemia can reduce cardiovascular morbidity and/or mortality in people at high risk for vascular diseases with either IFG, IGT, or early type 2 diabetes. To determine whether omega-3 polyunsaturated fatty acids (n-3 PUFAs) can reduce cardiovascular mortality in people with IFG, IGT, or early type 2 diabetes.

**STUDY DESIGN**

Multicenter, international, randomized, open-label (for insulin glargine versus standard care), double-blind (for n-3 PUFAs versus placebo), 2x2 factorial study.

Sample size: 9980 patients.

**STUDY POPULATION**

Participants must have one of the following: - History of coronary artery disease documented on a coronary angiography or by a previous myocardial infarction or a coronary revascularization, - Left ventricular systolic dysfunction defined as a left ventricular ejection fraction equal to 39% or lower on a two-dimensional echocardiography and a left ventricular dilatation defined as an echocardiographically measured short-axis internal dimension greater than 56 millimeters, - Sinus rhythm and resting heart rate equal to or higher than 60 beats per minute.

**STATE OF RECRUITMENT**

Up to May 13, 2005, 8184 patients have been recruited in 42 countries. In Italy, 103 patients have been randomized by 20 centers.

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**BEAUTIFUL**

**MorBidity-mortality EvALuATion of the IF inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction**

**Executive Committee:** K. Fox (Chairman), R. Ferrari (Co-Chairman), I. Ford, P.G. Steg, M. Tendera

**STUDY SUPPORTED BY INSTITUTE DE RECHERCHES INTERNATIONALES SERVIER (I.R.I.S.)**

**OBJECTIVES**

The purpose of this study is to demonstrate that ivabradine reduces cardiovascular events in patients with coronary artery disease and left ventricular systolic dysfunction. The primary objective is to demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality, hospital admissions for acute myocardial infarction, hospital admissions for new onset or worsening heart failure (composite endpoint).

**STUDY DESIGN**

Randomised, double blind, placebo-controlled, multi-center, international trial, with two parallel and balanced treatment arms. Sample size: 9650 patients.

**STUDY POPULATION**

The main inclusion criteria will be: - History of coronary artery disease documented on a coronary angiography or by a previous myocardial infarction or a coronary revascularization, - Left ventricular systolic dysfunction defined as a left ventricular ejection fraction equal to 39% or lower on a two-dimensional echocardiography and a left ventricular dilatation defined as an echocardiographically measured short-axis internal dimension greater than 56 millimeters, - Sinus rhythm and resting heart rate equal to or higher than 60 beats per minute.

**STATE OF RECRUITMENT**

Up to May 2005, 216 patients have been recruited in 32 countries. In Italy nearly 70 centers are participating in this trial. As of May 2005, 16 patients have been recruited in Italy.

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**SCOUT**

**Sibutramine Cardiovascular Morbidity/Mortality OUTcomes Study in Overweight or Obese Subjects at Risk of a Cardiovascular Event**

**Steering Committee:** P. James (Chairman), I. Caterson, W. Coutinho, N. Finer, A.P. Maggioni, A. Sharma, C. Torp-Pedersen, L. Van Gaal

**STUDY SUPPORTED BY ABBOTT LABORATORIES**

**OBJECTIVES**

To compare the effect of sibutramine with standard care for weight management to placebo with standard care for weight management on the incidence of a composite cardiovascular outcome comprised of non-fatal myocardial infarction, non-fatal stroke, rehospitalized cardiac arrest and cardiovascular death (including events such as fatal myocardial infarction and fatal stroke) in overweight or obese subjects at risk of a cardiovascular event.

**STUDY DESIGN**


**STUDY POPULATION**

Eligible subjects for this study are men and women, age 55 years and older, who have a BMI ≥27 kg/m² or <45 kg/m² or a BMI ≥25 kg/m² and <27 kg/m² with increased waist circumference and who are at risk of a cardiovascular event based on a history of documented cardiovascular disease, cerebrovascular disease, peripheral vascular disease or type 2 diabetes mellitus with at least one other risk factor.

**STATE OF RECRUITMENT**

Up to April 2005, 9112 patients have been recruited in 16 countries. In Italy, 171 patients have been randomized by 15 centers.

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**EVEREST**

**Efficacy of Vasopressin Antagonism in HEart Fai lure: Outcome Study with Tolvaptan**

**Steering Committee:** M. Konstam (Chairman), J. Burnett, M. Gheorghiade (Co-Chairmen), L. Grinfeld, A.P. Maggioni, K. Swedberg, F. Zannad

**STUDY SUPPORTED BY OTSUKA MARYLAND RESEARCH INSTITUTE**

**OBJECTIVES**

To compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the time to all-cause mortality in subjects hospitalized with worsening CHF.

**STUDY DESIGN**

Multicenter, randomized, double-blind, placebo-controlled. Sample size: 3600 patients.

**STUDY POPULATION**

Subjects hospitalized for worsening heart failure.

**STATE OF RECRUITMENT**

Up to May 2005, 1999 patients have been randomized by 30 centers.
CandHeart

Effects of CANDesartan cilexitil vs standard therapy on serum levels of brain natriuretic peptide in patients suffering from chronic HEart failure with depressed and preseRved systolic function

Steering Committee: G. Sinagra (Chairman), G. Cacciareto, R. Latini, A.P. Maggioni, G. Misuraca

STUDY ENDORSED BY ANMCO – STUDY SUPPORTED BY TAKEDA

RATIONALE

Despite the improvements in the management of chronic heart failure (CHF), the risk of death remains high for a consistent proportion of patients. There is a need to search for a prognostic markers able to predict outcomes. The angiotensin II type-1 receptor blockers (ARBs) significantly reduce BNP plasma levels; however, there are no formal evidences that a sustained reduction of circulating levels of BNP may result in a significant clinical benefit and, moreover, there are no available data in CHF patients with preserved LV systolic function.

STUDY DESIGN

Phase III, multi-centre, open-label, randomised trial designed to investigate the effects of candesartan, as compared to standard therapy, in a large CHF population, including patients with either preserved or reduced LV systolic function.

Population. 1,500 patients will be recruited in approximately 130 Italian Centres (100 Cardiology sites and 30 Internal Medicine sites) in order to have 650 assessable patients for each group. The eligibility criteria are:

- both genders,
- at least 1 cardiovascular hospitalisation during the past 18 years,
- stable NYHA IV/IV class CHF with any LVEF treated with standard therapy including ACE-inhibitors and/or beta-blockers; for patients with LVEF ≥40%, at least 1 cardiovascular hospitalisation during the past 12 months is required,
- written informed consent.

Dugs. Candesartan cilexitil (4 mg once daily up titrated to the maximum dosage of 32 mg/die, if tolerated) added to ongoing standard therapy for CHF, versus oral standard therapy (at dosages normally employed for CHF).

Duration. One-year.

Objectives. The primary objective of the study is to assess, after a 3-month treatment period, the effects of candesartan in addition to ongoing standard CHF therapy on circulating levels of BNP.

Secondary objectives of the study are to assess, after a 1-year treatment period, the effects of candesartan in addition to ongoing standard CHF therapy versus standard CHF therapy on:
- circulating levels of BNP (48 weeks),
- circulating levels of aldosterone, peroxin-3 (a protein associated with myocardial injury in patients with ischaemic cardiomyopathy), and C-reactive protein (a marker of inflammation and a prognostic factor in patients with ischaemic cardiomyopathy).

IN-ACS Outcome Steering Committee: A. Boccanelli (Chairman), S. Giampaoli (Co-chairman), L. Bolognese, F. Chiarella, G. Di Pasquale, A. Malfri, M. Scherrillo, C. Schweiger

STUDY PARTIALLY SUPPORTED BY SANOFI-AVENTIS AND BRISTOL-MYERS SQUIBB

In collaboration with the Istituto Superiore di Sanità

BACKGROUND

Ischaemic heart disease remains the primary cause of death in Italy and in western countries even if, in the last decades, many improvements have been achieved in the management and treatment of patients with Acute Coronary Syndromes (ACS). These results have been obtained due to the availability of new drugs and the development of interventional cardiology procedures, which have shown to be of great efficacy both in patients with ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI), particularly in those at high risk.

Due to the elevated costs of these procedures it is very important to assess and optimize their use in our country, so that these procedures will be used for those patients who really need them and will achieve most benefit from their use. In this setting it seems particularly interesting to collect data on the Italian situation in a specific registry and for this reason ANMCO has identified a Minimal Data Set of variables (MDS-ACS) which can be used for the creation of a database regarding patients with ACS.

DESCRIPTION

The registry has two parts both using the Minimal Data Set:

IN-ACS. The first collects general epidemiological data on the hospitalization phase. Nearly two hundred cardiology and medical centers will be part of this registry. In this setting to collect follow-up data is not mandatory and the clinical management of the patient is left to the individual clinical practice of each participating hospital.

IN-ACS Outcome. The second part, which involves a smaller, but representative sample of centers has the principal objective of describing the short and mid-term outcome of patients with ACS. In this part of the study, the participating centers, selected to be representative of the Italian situation with regard to their geographical distribution and technological level, must collect information on the patients' follow-up at 1, 3, 6 and 12 months from the time of enrolment in the registry.

IN-ACS Get Appropriate. Antiplatelet therapy is the leading therapy in patients with ACS without ST elevation undergoing or not to a revascularization procedure. Recently several clinical trials have markedly modified the management of patients with ACS, associated with at least one of the following:

- Acute ischaemic modifications at the ECG:
  - ST depression > or = 0.5 mm, transient ST elevation lasting <20 min, negative T waves >1 mm in at least two contiguous leads.
  - ST elevation, persistent at least 20 min, or >1 mm in two contiguous peripheral leads or >2 mm in two contiguous precordial leads.
  - Biochemical evidence of myocardial necrosis (CK-CMB, troponins)
  - Previous myocardial revascularization (PTCA or CABG) or documentation of CAD (coronary artery disease) with at least 50% stenosis of one of the major coronary vessels.
  - Documentation of previous myocardial infarction.

STUDY DESIGN AND STUDY POPULATION

The study is designed as a national, multicentre, observational study and foresees the collection of clinical data at baseline and during a follow-up period of one year, using a web-based system. The study population is composed of patients, with a diagnosis of ACS, admitted consecutively to cardiology and internal medicine wards participating to the study.

INCLUSION CRITERIA

Patients of any age that are admitted to the participating centers with a diagnosis of ACS within 48 hours of the last symptomatic episode, will be included in the study. We identify as necessary criteria for the diagnosis of acute myocardial ischaemia a compatible clinical presentation associated with at least one of the following:

- Acute ischaemic modifications at the ECG
- Previous myocardial revascularization (PTCA or CABG) or documentation of CAD (coronary artery disease) with at least 50% stenosis of one of the major coronary vessels.
- Documentation of previous myocardial infarction.
Left ventricular DYSfunction in DiAbetes
Epidemiological survey on incidence and prevalence of left ventricular dysfunction in diabetic patients without known cardiac disease

Working Groups: Heart Failure and Prevention

Steering Committee: M. Comaschi (Chairman), A. Di Lenarda (Co-Chairman), A. Ceriello, P. Faggiano, L. Tarantini, M. Velussi

SUBSTUDY ON LEFT VENTRICULAR DYSFUNCTION IN DIABETIC PATIENTS WITH ARTERIAL HYPERTENSION
G. Cioffi, G. De Simone, P. Faggiano (Coordinator), G.F. Mureddu, P. Verdeccia

STUDY PARTIALLY SUPPORTED BY SANOFI-AVENTIS
In collaboration with AMD (Associazione Medici Diabetologi)

BACKGROUND
Diabetes is a well known risk factor for heart failure and poses an additional risk to develop left ventricular dysfunction (LVD): in the community studies, LVD have twofold higher prevalence in diabetic than non diabetic subjects.

The presence of asymptomatic LVD in diabetics is frequent and is prognostically grim. In the Cardiovascular Health Study, at baseline evaluation, 40% of the 1343 diabetic participants (age >=5 years) had subclinical LVD and during the follow-up of 6.4 years those patients had higher mortality rate (relative risk 1.5) with respect to diabetic subjects without asymptomatic LVD.

Thus, there is the need to identify rational, practicable and cost-effective pathways to screen diabetic subjects at high risk to develop LVD in order to initiate an early appropriate and intensive cardiologic diagnostic and therapeutic plan.

STUDY DESIGN
Prospective, multicentric, nationwide epidemiological study. The screening and enrolment phase will last 12 months or until the enrolment of 1000 patients.

OBJECTIVES
Primary Objective.
To evaluate in patients with type II diabetes without documented heart disease, the prevalence of diastolic and/or systolic left ventricular dysfunction (ejection fraction <50% and/or diastolic abnormalities at echocardiogram at enrolment) and to identify their predicting clinical, laboratory and non-invasive instrumental parameters.

Secondary Objective.
1) to evaluate the incidence of systolic and/or diastolic LVD in patients with normal ventricular function at enrolment,
2) to evaluate the incidence and types of ECG abnormalities in patients with normal ECG at baseline,
3) to evaluate two year all-cause mortality and hospitalization for cardiovascular causes.

STUDY POPULATION
Inclusion Criteria
1) Patients with type II diabetes (according to WHO criteria)
2) No history of heart disease
3) Age > 45 years
4) Written consent form

STUDY SETTING
Forty Italian Centres for the care of diabetes mellitus. A reference cardiology center will be associated to each Diabetology center to perform instrumental cardiologic evaluations. Interpretation of findings from instrumental examinations such as ECG, echocardiogram, and from blood samples analysis such as BNP, Hba1c and hs-CRP at baseline and after two-years of follow up will be done by the Core Lab.

Registry: Diabetic patients who will be screened for the study and who will be not eligible because of previous documentation of heart disease will be enclosed in the Registry for Diabetic Patients with known cardiac disease.

Study duration: Two years for each patient enrolled.

The G8 cardio program has been moved on the WEB (G8-CardioWeb). Compared to the old project the web version will give the following advantages:

- possibility to enlarge the network of centers that can adhere to the project and collect data through the system,
- easiness in the management of addition and changes to the program,
- on-line help-desk feature, including account management and task suggestions,
- on-line ordinary reports and self-data analysis through pre-ordinate queries.

Beside its use as a tool for daily clinical practice in the different cardiological settings (from CCU, to Cath and EP lab, from Echo-Lab to outpatients clinics) the G8-CardioWeb is a unvaluable tool for permanent or ad hoc registries.

The necessity to develop data standard (variables, definition, etc.) has been lately felt of great importance to create registries to improve the quality of patient care and the efficiency of cardiology service. The collection and analysis of comparable data would also provide a context in which to interpret local and national data.

ANMCO with other scientific Societies has therefore instituted ad hoc commissions (one for every specific Topic) to define which data could be considered essential (core of data) to a specific cardiological field. These data are defined as Minimal Data Set. All these data (MDS) are part of the G8 Cardio Program therefore those who will use it will automatically collect these data.

Forthcoming national registries are: IN-ACS (Italian Network of Acute Coronary Syndromes), IN-ACS Outcome, IN-CP.

For those centers using own institutional software, and hence not interested in the G8 program but only in the creation of registries, there will be designed hoc software for extracions of Minimal Data Sets, and merging with the central ANMCO database. The creation of registry can also provide a basis for health service planning and for epidemiological research.

The diagram below describes a flow of information ANMCO is trying to propone.