Fondazione Italiana per la Lotta alle Malattie Cardiovascolari - ONLUS
Costituita dall’Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)

ANMCO Research Center Activities 2008
ANMCO is the Italian Association of Hospital Cardiologists, a non-profit professional association of over 4100 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 (HCF), legally recognized by the Ministry of Health on September 2000. HCF is registered in the ONLUS registry. The aim of the foundation is 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.

The ANMCO Research Center of HCF has received on December 22, 2005 the certification UNI EN ISO 9001:2000 for the planning, development, management and coordination of research projects in the biomedical field.

The ANMCO Research Center is coordinating a clinical Network of:

- **4131** Cardiologists
- **880** Cardiology Centers
- **44** Diabetology Centers
- **80** Internal Medicine Divisions

This large network of 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 diseases 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 also co-ordinated 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.
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 conduction of most of the studies approved by the ANMCO board.

SELECTED REFERENCES OF YEAR 2007


IN-HF Outcome
Italian Registry on Heart Failure (IN-HF) Outcome

IN-HF Outcome Steering Committee: L. Tavazzi (Chairman), G. Cacciatore, A. Chinaglia, A. Di Lenarda, A.P. Maggioni, M. Metra, A. Mortara, F. Oliva, M. Senni

STUDY PARTIALLY SUPPORTED BY NOVARTIS, MEDTRONIC AND ABBOTT

STUDY DESIGN
Prospective, non-interventional, multicentric observational study in patients with chronic (CHF) and acute heart failure (AHF).

MAIN STUDY OBJECTIVES
To describe the diagnostic and pharmacological/non-pharmacological therapeutic approaches undertaken in the routine practice of cardiologists in following out-patients with CHF and during the hospital phase for AHF. To assess the in-hospital and out-of-hospital outcome of patients with CHF and AHF and the prognostic predictors of this outcome.

STUDY POPULATION
Outpatients with CHF diagnosed according to the ESC guidelines. Patients admitted for AHF and treated with IV therapy. Subpopulations of HF patients will be specifically focused with larger and more detailed data collection:
- Patients with HF in whom ICD, CRT or both are implanted during the course of the study.
- Patients admitted for AHF with a history of hypertension and a SBP >160 mmHg.
- Patients admitted for AHF and treated with IV inotropic or vasodilator agents.

ENROLLMENT AND FOLLOW-UP PERIOD
The enrollment will last twelve months. Each included patient will be followed-up for 1 year. Patients with HF and patients with AHF treated with IV inotropes or vasodilators and those admitted for hypertensive HF will be followed-up at 3, 6 and 12 months.

SAMPLE SIZE
A formal sample size was not calculated. With respect to the different categories of patients the expectations in terms of numerosity are reported below:
- CHF: approximately 2500-3500 patients.
- AHF: approximately 225 patients.
- Subgroup of patients with hypertension: approximately 1300-1800 patients.
- Subgroup of patients with implanted devices: approximately 325-550 patients.
- Subgroup of patients admitted for AHF treated with IV inotropes or vasodilators: approximately 1500 patients.

STUDY ADVANCEMENT (as of May 5, 2008)
Study enrollment started on November 2007
Participating centers: 62
Activated centers: 34
Recruiting centers: 10
Enrolled patients: 225

TOP TEN

<table>
<thead>
<tr>
<th>Center</th>
<th>N. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roma, Ospedale S. Giovanni, U.O. Cardiologia</td>
<td>188</td>
</tr>
<tr>
<td>Ascoli Piceno, Osp. Gen.le Prove, Divisione di Cardiologia</td>
<td>53</td>
</tr>
<tr>
<td>Albano Laziale, Osp. Riuniti Albano-Cenzano, U.O.C. di Cardiologia</td>
<td>25</td>
</tr>
<tr>
<td>Passirana-Rho, Presidio Ospedaliero,Divisione di Cardiologia</td>
<td>19</td>
</tr>
<tr>
<td>Lumezzane, Fondazione Salvatore Maugeri, U.O. di Cardiol. Riabil.</td>
<td>16</td>
</tr>
<tr>
<td>Napoli, Ospedale Incurabili, Divisione di Medicina</td>
<td>14</td>
</tr>
<tr>
<td>Firenze, Nuovo Ospedale San Giovanni di Dio, U.O. Cardiologia</td>
<td>12</td>
</tr>
<tr>
<td>Firenze, Az. Ospedaliero-Universitaria, Cardiologia Generale 1</td>
<td>10</td>
</tr>
<tr>
<td>San Pietro Vernotico, Ospedale N. Meli, U.O. Semplice Cardiologia</td>
<td>8</td>
</tr>
<tr>
<td>Brescia, Spedali Civili, Divisione di Cardiologia</td>
<td>7</td>
</tr>
</tbody>
</table>
GISSI-HF

A large scale clinical trial testing the effects of n-3 PUFA and statins on mortality/morbidity of patients with symptomatic chronic Heart Failure

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

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

In collaboration with Mario Negri Institute, Milan, Italy and Consorzio Mario Negri Sud, S. Maria Imbaro, Italy

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 n-3 PUFA and (b) a lipid lowering agent on top of the best recommended treatments for heart failure.

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 any reason
• Sudden cardiac death
• Hospitalizations for any reason
• Hospitalizations for cardiovascular reasons
• Hospitalizations for congestive heart failure
• Myocardial infarction
• Stroke

ENTRY CRITERIA

• Clinical evidence of heart failure according to the ESC guidelines (NYHA class II-IV)
• Any left ventricular EF measured within 3 months from enrolment (EF >40%, at least 1 hospital admission for HF in the previous year)
• No age limits
• Any etiology
• Informed consent

COMMON EXCLUSION CRITERIA (R1=n-3 PUFA vs placebo and R2=rosuvastatin vs placebo):- AML, unstable angina or revascularization procedure within 1 month;
- planned cardiac surgery, expected to be performed within 3 months;
- congenital or primary valvular etiology;
- known hypersensitivity to study treatments;
- significant liver disease;
- pregnant or lactating women or women of childbearing potential not protected from pregnancy by an accepted method of contraception;
- 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;
- presence of any non-cardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy;
- treatment with any investigational agent within 1 month before randomization;
- patients already on treatment with n-3 PUFA or statin for whom the prescription is confirmed.

EXCLUSION CRITERIA FOR R2 (statin hypothesis):

• current CPK upper normal limits.
• current ALT, AST level >1.5 times the upper normal limit;
• current serum creatinine level >2.5 mg/dL;
• patients already on treatment with n-3 PUFA or statin for whom the prescription is confirmed.

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. Patients enrolled in each trial will be followed until the occurrence of a sufficient number of deaths in R2 unless the trial is stopped early on the basis of the interim analysis or of new scientific evidences. All primary end points will be validated centrally by an ad-hoc committee (E. Geraci, M. Scherillo, D. Bertoli, F. Cobelli, C. Fresco, A. Ledda, C. Leventi, C. Opasich, F. Rusconi, G. Sinagra, F. Turazza, A. Volpi).

GISSI-HF SUBPROJECTS

Final status on substudies

<table>
<thead>
<tr>
<th>Substudy</th>
<th>Active centers</th>
<th>Pts with at least 1 exam (number, % of target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography (M. Scherillo, D. Bertoli)</td>
<td><a href="mailto:echocardiography@marionegri.it">echocardiography@marionegri.it</a></td>
<td>287 579 (200%)</td>
</tr>
<tr>
<td>Microalbuminuria (R. Latini, S. Masson)</td>
<td><a href="mailto:microalbuminuria@marionegri.it">microalbuminuria@marionegri.it</a></td>
<td>197 3953 (25%)</td>
</tr>
<tr>
<td>Exercise (U. Corrà)</td>
<td><a href="mailto:exercise@marionegri.it">exercise@marionegri.it</a></td>
<td>257 514 (100%)</td>
</tr>
<tr>
<td>Holter (M.T. La Rovere)</td>
<td><a href="mailto:holter@marionegri.it">holter@marionegri.it</a></td>
<td>76 1533 (22%)</td>
</tr>
<tr>
<td>Quality of life (P. Di Giulio)</td>
<td><a href="mailto:qualityoflife@marionegri.it">qualityoflife@marionegri.it</a></td>
<td>146 2926 (105%)</td>
</tr>
<tr>
<td>Genetic (M.G. Franzosi, L. Crociati)</td>
<td><a href="mailto:genetic@marionegri.it">genetic@marionegri.it</a></td>
<td>128 2560 (125%)</td>
</tr>
<tr>
<td>Blood (R. Latini, S. Masson)</td>
<td><a href="mailto:blood@marionegri.it">blood@marionegri.it</a></td>
<td>199 3986 (201%)</td>
</tr>
</tbody>
</table>

STUDY ADVANCEMENT (as of May 2, 2007)

- Participating Centres: 356
- Patient Enrolled: 6975
- Enrollment: August 2002-February 2005

<table>
<thead>
<tr>
<th>R1 (n-3 PUFA vs Placebo)</th>
<th>R2 (Rosuvastatin vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>5459 (78.3%)</td>
</tr>
<tr>
<td>Age (mean±SD) yrs</td>
<td>67.2±10.7 (range 18-97)</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>2964 (42.5%)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>4424 (63.4%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>2365 (33.9%)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>185 (2.7%)</td>
</tr>
<tr>
<td>CHD etiology</td>
<td>3467 (49.7%)</td>
</tr>
<tr>
<td>EF% (mean±SD)</td>
<td>33.1±8.5 (range 10-87)</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>654 (9.4%)</td>
</tr>
</tbody>
</table>

TOTAL DEATHS

| R1 | 1964/6975 (28.2%) |
| R2 | 1297/4574 (28.4%) |

Final results will be presented at the next ESC Congress in Munich (August 30 - September 3, 2008)
CENSUS OF THE CARDIOLOGY CENTERS OF THE ITALIAN NATIONAL HEALTH SERVICE

STUDY ENDORSED BY THE ITALIAN FEDERATION OF CARDIOLOGY (FIC)
In collaboration with the Italian Society of Cardiology (SIC)
PARTIALLY SUPPORTED BY MERCK SHARP & DOHME

AIMS
♥ Describe the distribution of Italian Cardiology Centers. The survey included:
- University centers
- Hospital centers
- Private hospital centers with beds operating within the Italian National Health Service
♥ Describe the organization, the activities and the services provided by each cardiology center in the year 2005. Qualitative and quantitative data have been collected in terms of:
- Number and territorial distribution of Coronary Care Units (CCU)
- Cardiology beds:
  - CCU beds
  - Other cardiology beds
- Cardiac catheterization laboratories (with/without interventional section)
- Electrophysiology laboratories
- Nuclear cardiology laboratories
- Specific outpatients cardiology clinics:
  - Pacemaker
  - Hypertension
  - Heart Failure
  - Pediatric
  - Epidemiology and prevention
♥ Describe the type of routine non invasive examinations performed in each center: simple (echo, stress test, Holter) and more complex (stress echo, transesophageal echo, transesophageal electrophysiology).

METHODS
On March 2006 a letter was sent to the heads of the 843 Italian Cardiology centers informing them of the interest for a new census survey based on the data of year 2005. Each center received a user name and a password to enter the data of the census using a WEB based system.

RESULTS
The rate of reply was 92% (773/843 Centers: 93% Hospital; 89% University and 84% Private Hospital) and provides a complete picture of the cardiology network in the Italian Health Service (Figure 1).

There is a cardiology center in 728 (48%) out of 1503 Italian hospitals. Out of these 728 hospitals 55% have CCU, 32% a Cath Lab (90% with PCI facility). There are 83 (11%) hospitals with Cardiosurgery. In 70 hospitals (10%) there are CCU, Cath Lab and Cardiosurgery together. In Table 1 the number of hospital with cardiology center and Nuclear Medicine and with Electrophysiology facilities is also reported.

The number of CCUs and CCUs beds/population overall in Italy (1 CCU/136577 and 1 CCU bed 1/21816) and in the 21 Italian regions are reported in Figure 2. The historical gap between North and South is no more present.

The number of physicians operating in the 773 centers who replied to this questionnaire is 6915. The mean number of physicians operating in Hospital, University and Private centers and in any different type of cardiology centers is reported in Figure 3. The mean number varies in relation to the complexity of the centers ranging from 3.65 physicians for the centers without beds to 15.44 physicians for the centers with CCU and Cath Lab.

<table>
<thead>
<tr>
<th>Hospitals with cardiology centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCU</td>
</tr>
<tr>
<td>Cath Lab</td>
</tr>
<tr>
<td>PCI h 24</td>
</tr>
<tr>
<td>Cardiosurgery</td>
</tr>
<tr>
<td>CCU+Cardiac Lab</td>
</tr>
<tr>
<td>Cardiac cath Lab</td>
</tr>
<tr>
<td>Nuclear Medicine</td>
</tr>
<tr>
<td>Electrophysiology Ablations</td>
</tr>
<tr>
<td>Inhabitants / CCU bed</td>
</tr>
</tbody>
</table>

1 CCU bed every 21816 inhabitants – 1 CCU every 136577 inhabitants

<table>
<thead>
<tr>
<th>Mean number of physicians in the cardiology centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy Mean: 9.55</td>
</tr>
<tr>
<td>Hospital: 6.86</td>
</tr>
<tr>
<td>University: 13.79</td>
</tr>
<tr>
<td>Private: 6.65</td>
</tr>
<tr>
<td>Without bed: 9.77</td>
</tr>
<tr>
<td>With bed: 15.44</td>
</tr>
<tr>
<td>Without CCU: 6.65</td>
</tr>
<tr>
<td>With CCU: 9.77</td>
</tr>
<tr>
<td>With CCU bed: 15.44</td>
</tr>
</tbody>
</table>

Figure 1

Figure 2
Epidemiology of the hospitalizations in the Italian Coronary Care Unit network

Working Group on Emergency/Urgency

Steering Committee: L. Oltrona Visconti (Chairman), F. Chiarella, M. Cassin, A. Chinaglia, S. Pirelli, G. Scorcu, G. Casella, M.R. Conte, G. Fradella

STUDY PARTIALLY SUPPORTED BY NOVARTIS, BOEHRINGER-INGELHEIM, SANOFI-AVENTIS

RATIONALE

The current worldwide scientific cardiology community shares a consensual opinion on the relevance of prospective registries, due to the reliable description of the epidemiological profile and therapeutic management of the patients of real clinical practice, that randomized trials generally do not appropriately represent. On the same time, the role of the Intensive Heart Care Unit (IHCU) has changed: nowadays various cardiovascular pathologies like cardiogenic shock, acute heart failure, arrhythmias, pulmonary embolism, myocarditis, post-coronary angiography follow-up added to acute coronary syndromes, but precise prevalence is still unknown. There is also no evidence regarding the admission rate, the most frequent diagnosis, the patients-flow between Department Emergency Admission (DEA), 118 and IHCU, the follow-up in other units or other hospitals.

OBJECTIVES AND METHODS

The present study as the aim to describe the epidemiological profile of the current admission in the IHCU, the main aspects of the clinical patients’ management including “the road map” after the acute phase (transfer to other Departments), the short-term outcome, the prevalence of the most important co-morbidities (diabetes, kidney failure, broncho-pulmonary obstructive disease) and furthermore, the implications in terms of resource absorption. The diagnostic procedures and therapeutic options have been registered in a case-report web-based form.

INCLUSION CRITERIA

All patients admitted in the participating IHCU from April 7 to 20, 2008.

EXCLUSION CRITERIA

Only the patients who refused their written informed consent were excluded.

THERAPEUTIC OPTIONS

Being fully observational, the study did foresee neither specific pharmacological/non-pharmacological treatments nor specific invasive/non invasive diagnostic procedures, but the patients’ management was left to the decisions of the enrolling cardiologists.

PRELIMINARY RESULTS

6986 consecutive admissions were registered by 332 Italian IHCU, well representing the existing IHCU in Italy.

<table>
<thead>
<tr>
<th>Type of hospital</th>
<th>Italian IHCU n.</th>
<th>Participating Italian IHCU n. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>409</td>
<td>332 (81%)</td>
</tr>
<tr>
<td>North</td>
<td>169</td>
<td>135 (80%)</td>
</tr>
<tr>
<td>Center</td>
<td>97</td>
<td>77 (79%)</td>
</tr>
<tr>
<td>South</td>
<td>143</td>
<td>120 (84%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
</tr>
<tr>
<td>Age (mean±SD), years</td>
</tr>
<tr>
<td>All-cause mortality in IHCU</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most frequent diagnosis at discharge from IHCU</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
</tr>
<tr>
<td>NSTEMI/Unstable Angina</td>
</tr>
<tr>
<td>Heart Failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of stay in IHCU (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All admissions median [25%, 75%]</td>
</tr>
<tr>
<td>Patients with STEMI median [25%, 75%]</td>
</tr>
<tr>
<td>Patients with NSTEMI/Unstable Angina median [25%, 75%]</td>
</tr>
<tr>
<td>Patients with Heart Failure median [25%, 75%]</td>
</tr>
</tbody>
</table>
GISSI-AF

Randomized, prospective, multicenter study on the use of 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 (AF) recurrence with antiarrhythmic agents is very limited, given 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 AF initiation and maintenance. Moreover, some preliminary clinical data show that ARBs can prevent AF episodes. GISSI-AF is a randomized, prospective, parallel group, placebo-controlled, multicenter study designed to test whether ARBs can reduce AF recurrence.

OBJECTIVES AND METHODS

Primary objective of the study is to demonstrate that, in patients with history of recent AF treated with the best recommended therapies, the addition of the ARBs valsartan (titrated up to 320 mg) is superior to placebo in reducing: 1. first recurrence of AF, 2. rate of patients with more than one AF episode, over the whole follow-up. A substudy will analyse the effect of valsartan on left atrial dimensions and on neurohormones. The study population will consist of patients with symptomatic AF (at least 2 ECG documented AF episodes in the previous 6 months or successful cardioversion in the last 2 weeks) and having underlying cardiovascular diseases or comorbidities. The patients will be randomized in a 1:1 ratio to receive valsartan or placebo. The patients will be followed for 12 months from study entry.

INCLUSION CRITERIA

1. Male and female patients with at least 40 years of age,
2. In sinus rhythm at randomization (for at least 48 h in case of electric or pharmacologic cardioversion),
3. At least two ECG documented episodes of symptomatic AF in the previous 6 months, or Successful cardioversion for AF between 14 days and 48 hours before randomization,
4. At least one of the following:
   a) HF or documented history of LV dysfunction (defined as an EF <40%),
   b) History of hypertension ≥6 months with or without LVH,
   c) Type II diabetes mellitus,
   d) Documented history of stroke or peripheral vascular disease,
   e) Documented history of coronary artery disease,
   f) Lone AF with documented LA dilation (LA diameter >45 mm for men and ≥40 mm for women).
5. Informed consent.

EXCLUSION CRITERIA

1. Need for a continuous treatment with ARBs for any clinical reason,
2. Contraindications or known hypersensitivity to ARBs,
3. Persistent standing systolic blood pressure <110 mmHg,
4. Recent (<6 weeks) acute myocardial infarction or bypass surgery, or percutaneous coronary intervention,
5. Clinically significant valvular etiologies,
6. Thyroid dysfunction,
7. Indication for pacemaker or ICD implant or for an ablative treatment,
8. Indication for percutaneous coronary intervention,
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.

STUDY DESIGN

NUMBER OF PATIENTS TO BE RECRUITED

The GISSI-AF is the largest trial ever conducted aimed at assessing the role of ARBs in reducing recurrence of AF.

The sample size has been calculated with the following assumptions: AF recurrence over 1 year of follow-up in the control group= 50%, relative reduction of AF recurrence with valsartan =17.6 % (from 50% to 41.2 %), with 88% power and a 2s error of 0.04. 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.

STUDY ADVANCEMENT (as of May 5, 2008)

Randomization closed on January 14, 2007
Follow up period closed December 31, 2007
Recruiting centres: 114 Patients enrolled: 1442

CHARACTERISTICS OF ENROLLED PATIENTS (n. 1442)

Female 37.7%
Age mean (mean±DS) years 67.8±9.2 (range 40-92)
Age >70 years 44.5%
At least 2 episodes of AF in the last 6 months 24.2%
CVA in the last 2 weeks 60.4%
Both criteria: 15.4%

QUALITY SCORE TOP TEN

<table>
<thead>
<tr>
<th>Hospitals</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergamo, USC Cardiologia, Ospedali Riuniti</td>
<td>10.0</td>
</tr>
<tr>
<td>SanBonifacio, UOC Cardiologia, Ospedale G. Fracastoro</td>
<td>10.0</td>
</tr>
<tr>
<td>Terni, UO Cardiologia Torritie, Azienda USL 4 Terni</td>
<td>10.0</td>
</tr>
<tr>
<td>San Daniele del Friuli, UOS Cardiologia, Ospedale S. Antonio</td>
<td>9.7</td>
</tr>
<tr>
<td>Roma, Divisione di Cardiologia e UTIC, Osp. S. Filippo Neri</td>
<td>9.7</td>
</tr>
<tr>
<td>Cosenza, Divisione di Cardiologia, Ospedale SS. Annunziata</td>
<td>9.7</td>
</tr>
<tr>
<td>Catania, UOC di Cardiologia, Ospedale Garibaldi-Nesima</td>
<td>9.7</td>
</tr>
<tr>
<td>Milazzo, Servizio di Cardiologia, Pres. Ospedaliero ‘G. Fogliani’</td>
<td>9.7</td>
</tr>
<tr>
<td>Cles, Medicina Interna, Ospedale di Cles</td>
<td>9.7</td>
</tr>
<tr>
<td>Bari, UO di Cardiologia Ospedaliera, Osp. Cperziale Policlinico</td>
<td>9.5</td>
</tr>
</tbody>
</table>
Italian Study on the Cardiovascular Effect of Systolic Blood Pressure Control

**Working Group: Prevention**

**Steering Committee:** P. Verdecchia (Chairman), J.A. Staessen, A. Achilli, G. De Simone, A. Ganau, G. Mureddu, S. Pede

**STUDY PARTIALLY SUPPORTED BY BOEHRINGER-INGELHEIM, PFIZER, SANOFI-AVENTIS**

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

---

**RATIONALE**

Only a minority of treated hypertensive subjects achieve adequate BP control. Unfortunately, poor control of BP during treatment predicts a high risk of future cardiovascular disease. There is growing evidence that ECG changes in LVH during treatment are potent predictors of outcome. In the Framingham Heart Study, subjects with baseline LHV and serial increase over time in the ECG voltages were twice as likely to suffer a cardiovascular event over the subsequent years when compared with those with a decrease in the voltages.

There is no evidence from prospective, randomised, controlled studies that a therapeutic strategy aimed to achieve a tighter control of systolic BP (for example: < 130 mmHg) will result in a greater reduction in LHV than a usual strategy (systolic BP reduction < 140 mmHg).

**STUDY OBJECTIVE**

Aim of the study is to ascertain whether an intensive treatment strategy finalized to decrease office systolic BP < 130 mmHg is superior to the usual strategy focused on lowering systolic BP < 140 mmHg in hypertensive subjects aged ≥ 55 years and poorly controlled (office systolic BP 150 mmHg), in terms of favourable change in ECG criteria for LHV. Patients with concomitant diabetes or renal failure will be excluded from this study because achievement of a tight BP control in these patients is already supported by existing evidence. LHV at ECG will be assessed by the Perugia score. The primary point for the comparison between the two groups will be the change in LHV 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 secondarily sera of the subjects who achieved the target BP (< 140 mmHg and < 130 mmHg) by protocol-analysis.
3. To perform the following pre-specified sub-group analyses:
   - 3.1. Absence vs presence of LHV at randomization.
   - 3.2. Age ≥ 70 years at randomization.
   - 3.3. Men vs Women.
4. To compare the 2 groups in the continuous (Cornell voltage) and non-continuous (strain, Romhilt-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 2 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.).
8. To compare the 2 groups in the continuous (Cornell voltage) and non continuous (strain, Romhilt-Estes) components of the Perugia score.

**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.
5. Any disease causing reduced life expectancy.
6. Unwilling to participate.
7. 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 study to the clinical practice, the use of specific anti-hypertensive 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 [amilpril 5 mg + hydrochlorothiazide 23 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 sympathetic inhibiting drugs: clonidine (transdermal) [2 mg].

**STUDY ADVANCEMENT**

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

Study enrollment started on February 2005.

Study enrollment closed on February 2007.

Patients expected: 1100

Activated Centers: 50

Randomizing Centers: 44

Randomized Patients: 1111

Patients who already concluded the study: 484

---

**Baseline characteristics**

| Clinical and demographic variables | Randomized Patients randomized Patients randomized Patients randomized to Usual strategy to Intensive strategy to Usual strategy to Intensive strategy to Usual strategy to Intensive strategy |
|-----------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Age (years)* | 66 (7) | 66 (7) | 66 (7) |
| Male (%) | 41 | 41 | 41 |
| Weight (kg) (mean) | 74 | 74 | 74 |
| Height (cm) (mean) | 163 | 163 | 163 |
| SBP at visit 1 (mmHg)* | 162 (11) | 162 (11) | 162 (11) |
| DBP at visit 1 (mmHg)* | 89 (9) | 89 (9) | 89 (9) |
| HR at visit 1 (bpmm)* | 70 (10) | 70 (10) | 70 (10) |
| Prevalence of risk factors | 21 | 20 | 21 |
| Cigarette smoking (%) | 75 | 74 | 74 |
| Hypertension (%) | 27 | 28 | 28 |
| Previous history of CV disease (%) | 8 | 8 | 7 |
| Coronary artery disease (%) | 11 | 12 | 10 |
| Claudication interstitial (%) | 2 | 2 | 1 |
| Laboratory Examination | 2 | 3 | 2 |
| creatinine (mg/dl)* | 0.94 (0.23) | 0.94 (0.22) | 0.94 (0.23) |
| Glucose (mg/dl)* | 97 (13) | 97 (11) | 97 (14) |
| Uric acid (mg/dl)* | 3.8 (4.3) | 3.9 (4.9) | 3.7 (3.7) |
| Total Cholesterol (mg/dl)* | 162 (44) | 167 (45) | 213 (59) |
| HDL Cholesterol (mg/dl)* | 57 (20) | 57 (20) | 57 (20) |
| LDL Cholesterol (mg/dl)* | 150 (36) | 150 (40) | 150 (37) |
| Triglycerides (mg/dl)* | 140 (80) | 143 (88) | 137 (72) |

* mean (± SD)
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), P. Faggiano, C. Giorda, 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. Verdecchia

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 patients (age >65 years) had subclinical LVD and during the follow-up of 6.4 years had higher mortality rate (relative risk 1.5) with respect to diabetic subjects without asymptomatic LVD.

Thus, there is the need to identify practicable and cost-effective pathways to screen diabetic subjects at high risk to develop LVD in order to initiate an early appropriate and intensive 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 enrollment 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 at two years in patients with normal ventricular function at baseline, 2) to evaluate the incidence and types of ECG abnormalities at two years 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
The study will be performed in 40 Italian Diabetology Centres. Each Center will be associated to a reference cardiology unit where instrumental cardiology evaluation will be performed. Each Centre will have to enrol at least 30 patients.

Interpretation of findings from instrumental examinations such as ECG, echocardiogram, and from blood samples analysis such as BNP, HbA1c, hs-CRP and microalbuminuria at baseline and after two-years of follow up (only for ECG and echocardiogram) will be done by a central Core Lab.

Registry. For seven days, before the beginning of the enrolment period, each diabetology center will keep a registry of all patients visited.

Study duration: Two years for each patient enrolled.

STUDY ADVANCEMENT (as of May 5, 2008)
Enrollment: July 2006 - March 2008
Participating centers: 37
Enrolled patients: 970
The follow up period is ongoing

Baseline characteristics of 970 enrolled patients

<table>
<thead>
<tr>
<th>Males</th>
<th>603 (62.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD) years</td>
<td>62±7.7</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>144 (14.9%)</td>
</tr>
</tbody>
</table>

TOP TEN

<table>
<thead>
<tr>
<th>Center</th>
<th>n. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Termini, A.O. Santa Maria, Clinica Medica</td>
<td>51</td>
</tr>
<tr>
<td>Montecchio Emilia, Ospedale E. Franchini, Medicina Interna</td>
<td>50</td>
</tr>
<tr>
<td>Milano, Ospedale San Paolo, Medicina II</td>
<td>49</td>
</tr>
<tr>
<td>Chieri, Ospedale Maggiore, Diabetologia</td>
<td>47</td>
</tr>
<tr>
<td>Brescia, Spedali Civili, U.O. Diabetologia</td>
<td>44</td>
</tr>
<tr>
<td>Mirano, Ospedale Civile, Medicina</td>
<td>44</td>
</tr>
<tr>
<td>San Benedetto del Tronto, Osp. Madonna del Soccorso, Diabetologia</td>
<td>40</td>
</tr>
<tr>
<td>Firenze, Nuovo Osp. San Giovanni di Dio, Diabetologia</td>
<td>40</td>
</tr>
<tr>
<td>Arenzano, Ospedale La Colletta, U.O. Diabetologia</td>
<td>37</td>
</tr>
<tr>
<td>Prato, Osp. Misericordia a Dolce, Diabetologia</td>
<td>35</td>
</tr>
</tbody>
</table>
IN-ACS OUTCOME

Italian Network on Acute Coronary Syndromes
Clinical epidemiology (and outcome) of patients hospitalized in Italy with acute coronary syndromes

Working Group: Acute Cardiac Care

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

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

In collaboration with the Istituto Superiore di Sanità

STUDY DESIGN AND STUDY POPULATION
The study is designed as a national, multicentre, observational study. Clinical data at base line and during a follow-up period of one year will be collected 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 in the study.

Duration: one year of enrolment for each centre, one year of follow-up for each patient (at 1, 3, 6 and 12 months).

AIM OF THE STUDY
To verify short and mid-term outcome of inpatients with ACS.
To obtain information on the management pathways of different medical centers.
To obtain information on the adherence to the current guidelines.

Inclusion Criteria
Patients of any age that are admitted to the participating centers with a diagnosis of ACS within 48 hours from the last symptomatic episode will be included in the study. We identify as necessary criteria for the diagnosis of acute myocardial ischaemia a typical clinical presentation 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, CK-MB, 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.

Patients who present ACS during elective revascularization procedures (PTCA or CABG) will also be enrolled.

Exclusion Criteria
- Patients who present ACS secondary to confounding comorbidities (such as car accidents, traumas or non cardiac surgery)
- No informed consent

Substudy 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 most relevant current guidelines. For this reason it seemed necessary to develop a substudy of IN-ACS Outcome to verify the rate of application of guidelines and the safety profile of the different antiplatelet therapies in the “real world” patients.

STUDY ADVANCEMENT (as of May 5, 2008)

41 Recruiting centers
32 CCUs
7 internal medicine
2 cardiology ward

Enrolment period December 2005-February 2008
Patients enrolled: 5892
Follow up period is ongoing

Clinical characteristics on 5869 patients

<table>
<thead>
<tr>
<th>2187 (37.3%)</th>
<th>3682 (62.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>NSTE-SCA</td>
</tr>
</tbody>
</table>

Baseline characteristics

<table>
<thead>
<tr>
<th>Females, %</th>
<th>30.6</th>
<th>28.7</th>
<th>31.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68±13</td>
<td>66±13</td>
<td>69±12</td>
</tr>
<tr>
<td>LDL-class, %</td>
<td>83.3</td>
<td>84.0</td>
<td>82.8</td>
</tr>
<tr>
<td>2</td>
<td>10.5</td>
<td>9.5</td>
<td>11.0</td>
</tr>
<tr>
<td>3-4</td>
<td>6.3</td>
<td>6.5</td>
<td>6.2</td>
</tr>
</tbody>
</table>

In-hospital treatment

<table>
<thead>
<tr>
<th>Coronary angiography</th>
<th>1850 (84.6%)</th>
<th>2733 (74.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>1600 (87.9%)</td>
<td>1738 (83.6%)</td>
</tr>
<tr>
<td>CABG</td>
<td>49 (2.2%)</td>
<td>205 (5.6%)</td>
</tr>
</tbody>
</table>

Lenght of stay

<table>
<thead>
<tr>
<th>Total Hospitalization (days)</th>
<th>6</th>
<th>6</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>(25%, 75%)</td>
<td>[4, 8]</td>
<td>[4, 8]</td>
<td>[4, 8]</td>
</tr>
<tr>
<td>Coronary Hospitalization (days)</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>(25%, 75%)</td>
<td>[2, 4]</td>
<td>[2, 4]</td>
<td>[2, 4]</td>
</tr>
</tbody>
</table>
Intensified Multifactorial Intervention on Hyperglycemic Patients with Acute Coronary Syndromes

**Steering Committee:** G. Casella (Chairman), S. Del Prato, G. Di Pasquale, C. Fresco, M. Galvani, C. Greco, C. Giorda, A.P. Maggioni, G. Steffenino

**STUDY PARTIALLY SUPPORTED BY PFIZER**

**BACKGROUND**

Despite the recent improvements of treatment of Acute Coronary Syndromes (ACS), hyperglycemia is still a marker of worse outcomes. This finding has been extensively demonstrated for patients either with ST-elevated myocardial infarction (STE-MI) or with non ST-elevated myocardial infarction (NSTEMI), whether diabetes has been previously diagnosed or not. Moreover, hyperglycemic patients without a previous history of diabetes have a higher mortality than diabetics when admitted for ACS. In addition, blood glucose level represents a continuous variable with respect to cardiovascular risk and even milder elevations portend a poor prognosis. During the last few years, several studies demonstrated that an intensive insulin treatment improves outcomes of hyperglycemic, critical patients, with or without previous history of diabetes. However, it is not clear whether these effects are the consequence of better glycemic control or result from a direct favorable actions of insulin. Moreover, diabetes and hyperglycemia represent the hallmark of a more complex metabolic condition. In fact, tight control of blood pressure, dyslipidemia and glucose in type 2 diabetic patients is associated with evident benefits, both in primary and secondary prevention. Thus, it is legitimate to expect that these beneficial effects may be translated in ACS patients with milder impairment of glucose homeostasis. In spite of all these evidences, ACS patients with impaired glucose tolerance and diabetes are still undertreated.

**AIM OF THE STUDY**

To evaluate the application of current evidence-based strategies (and therapies) in patients with blood glucose levels ≥200 mg/dl with ACS and to assess the efficacy of an intensified, targeted, multifactorial intervention strategy targeted to several modifiable risk factors in patients with ACS and abnormal glucose tolerance (blood glucose ≥140 mg/dl and <200 mg/dl) on admission.

**STUDY POPULATION**

Patients of any age, admitted to the Italian CCU network with ACS with or without ST elevation and troponin positive, <24 hours from symptom onset and blood glucose on admission ≥140 mg/dl.

**STUDY CHARACTERISTICS**

The study has two parts: 1. Observational (outcome study) 2. Multicenter, prospective, randomized, open-label study (active study)

1) **Outcome Study**

Patients with blood glucose levels on admission ≥200 mg/dl are enrolled in a 2-year observational, outcome study since current guidelines already recommend intensive medical treatment in such cases. All patients enrolled in the registry should be treated according to standard practice at local institutions and followed up for 2 years.

2) **Intensified, Multifactorial, Intervention Study**

Patients with or without known type 2 diabetes and blood glucose on admission ≥140 mg/dl and <200 mg/dl will be randomized (1:1) <24 hours from symptom onset to aggressive or conventional treatment strategies. The same intensified treatment of the index ACS will be implemented in both arms of the study during the acute phase.

1) **Intensified multifactorial intervention strategy arm.** Strict normalization of blood glucose levels during the acute phase of ACS (target fasting blood glucose: 80-110 mg/dl) will be pursued according to diabetologic consultations. After discharge, such patients should undergo intensive treatment of their cardiovascular disease and risk factors, aiming at therapeutic goals more stringent than that stated in the ADA 2005 guidelines.

2) **Conventional Care Treatment Arm.** Strict normalization of blood glucose levels is not requested (in-hospital target glucose levels <140 mg/dl). Patients are treated at discretion of the attending physician according to evidence-based international guidelines. Before discharge a secondary prevention program aiming at several modifiable risk factors with therapeutic goals similar to that stated by the JNC 7 guidelines is recommended.

**PRIMARY END POINT**

Composite end point of cardiovascular mortality, non fatal infarction, non fatal stroke or hospitalization for heart failure.

**SECONDARY END POINTS**

Several clinical and biochemical or metabolic end points have been planned either at 30-days or at 2 years follow-up.

**SAMPLE SIZE**

Since the trial is event driven the number of events which are needed to demonstrate the superiority of the intensive strategy is set at 347, for a study power of 90% at the significance level α=0.05. To reach this number of events we plan to enroll 1.500 patients over a period of 18 months.

**STUDY ADVANCEMENT (as of May 5, 2008)**

Study enrollment started on June 2007 Participating centers: 89 Enrolled patients in the Registry: 41 Activated centers: 44 Randomized patients: 45

**TOP TEN**

<table>
<thead>
<tr>
<th>Center</th>
<th>Registry Ps</th>
<th>Randomized Ps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuneo, A.O. S. Croce e Carle</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Pozzilli, Osp. S.M. Grazie</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Savigliano, Osp. Maggiore</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Teramo, Osp. Civile G. Mazzini</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bologna, Osp. Maggiore</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>L'Aquila, P.O. S. Salvatore</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Parma, A.O. Universitaria</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Rieti, P.O. San Camillo</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Giugliano in Campania, Osp. Gen.le</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Piombino, Osp. Villamarina</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
STUDIES ENDORSED BY ANMCO

CandHeart

Effects of CANDesartan cilextil 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. Cacciatore, R. Latini, A.P. Maggioni, G. Misuraca

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 prognostic markers able to predict outcome. The B-type brain natriuretic peptide (BNP), the only hormone synthesized in the heart and released in response to increased ventricular wall stress, has been found to be a highly sensitive and specific marker for cardiac dysfunction. Its circulating levels in patients with CHF have been shown to be related to the severity of the disease and mortality. 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 on CHF patients with preserved LV systolic function.

STUDY DESIGN

Phase III, multi-center, 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. 1500 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:
- age ≥18 years,
- both genders,
- stable NYHA II-IV class CHF with any LVEF, treated with standard CHF therapy versus standard CHF therapy, on oral standard therapy (at dosages normally employed for CHF).

Objective. 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 versus standard CHF therapy, on circulating levels of BNP.

Secondary objectives of the study are to assess, after a 48-week treatment period:
- circulating levels of BNP (48 weeks),
- circulating levels of aldosterone, pentraxin-3 (a protein considered as an early indicator of myocardial irreversible injury in patients with ischaemic cardiomyopathy), and C-reactive protein (a marker of inflammation and a prognostic factor in patients with ischaemic cardiomyopathy),
- NYHA functional class and quality of life,
- LV dimensions, systolic and diastolic function.

Design. Patients satisfying all the inclusion criteria and none of the exclusion criteria will be enrolled in the study, being centrally randomised either to candesartan added to their ongoing standard therapy for CHF (group 1) or to the prosecution of their ongoing standard therapy for CHF (group 2).

In order to allow for a sufficient number of CHF patients with preserved LV systolic function (defined as LVEF ≥40%) to be enrolled, approximately one third of the patients at each site should belong to this group.

STUDY SUPPORTED BY NOVARTIS

ALOFT

A twelve-week, randomized, double-blind, multi-center, placebo controlled, parallel group study to evaluate the safety and efficacy of aliskiren 150 mg when added to standard therapy in patients with stable heart failure

Steering Committee: B. Pitt, J.J.V. McMurray, R. Latini, A.P. Maggioni

STUDY SUPPORTED BY SANOFI

OBJECTIVES

The primary objective of this study is to evaluate the overall safety and tolerability of aliskiren when given in addition to standard therapy in hypertensive patients with stable heart failure. The study is further designed as an evaluation of the safety and efficacy (neurohormonal biomarkers, cardiac hemodynamics, symptomatic relief of heart failure, quality of life and quality of life assessments) of aliskiren. This study will provide a preliminary evidence on cardiac dysfunction. Its circulating levels in patients with CHF have been shown to be related to the severity of the disease and mortality. 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 on CHF patients with preserved LV systolic function.

STUDY DESIGN

This is a 12 week, randomized, double-blind, multi-center, placebo controlled, parallel group study to evaluate the safety and efficacy of aliskiren (150 mg OD) versus placebo when added to standard therapy in hypertensive patients with stable heart failure.

STUDY POPULATION

Men and women with essential hypertension and stable heart failure, and a baseline BNP >150 pg/mL. Overall 302 patients have been included. In Italy, 105 patients have been randomized by 25 centers. Final results were presented at the ESC Congress held in Wien in September 2007.

SUMMARY AND CONCLUSIONS

Aliskiren effectively inhibited plasma renin activity, even though most patients were treated with a beta-blocker. Adding the direct renin inhibitor, aliskiren, in patients also treated with an ACE inhibitor (or ARB) and, in a third of cases an aldosterone antagonist, appeared to be well tolerated.

Aliskiren had favourable neurohumoral actions, reducing plasma NT-pro BNP, plasma BNP and urinary aldosterone. The potential therapeutic role of aliskiren as alternative or "add-on" therapy to an ACE inhibitor (or ARB) in HF is worth investigating further.

Pre-specified safety assessments

<table>
<thead>
<tr>
<th>Assessment, n (%)</th>
<th>Placebo (n=144)</th>
<th>Aliskiren 150 mg (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction</td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Systolic hypertension</td>
<td>2 (1.4)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>7 (4.9)</td>
<td>19 (13.3)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>11 (7.7)</td>
<td>17 (12.0)</td>
</tr>
</tbody>
</table>

Perspective

A中
**SCOUT**

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

**Operational Committee**: P. James (Chairman), I. Caterson, W. Coutinho, N. Finer, A.P. Maggioni, J. Probstfield, A. Ramachandran, M. Riddle, L. Ryden

**STUDY SUPPORTED BY SANOFI-AVENTIS PHARMACEUTICALS**

**OBJECTIVES**

Moderate weight loss impacts positively on multiple cardiovascular risk factors. The SCOUT study has been designed 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 of nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest and cardiovascular death in overweight or obese subjects at risk of a cardiovascular event.

**STUDY DESIGN**

Double-blind, randomized, placebo-controlled, parallel-group, international, multicenter study with a single-blind, sibutramine lead-in period. Sample size: 9000 patients.

**STUDY POPULATION**

Eligible subjects for this study are men and women, age 55 years and older, who have a BMI >27 kg/m² and <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 THE STUDY**

The recruitment phase has been completed with the inclusion of 10765 patients in 16 countries. In Italy, 149 patients have been randomized by 44 centers. Final results will be likely presented during the next ESC Congress in Munich.

**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-centre, international trial, with two parallel and balanced treatment arms. Sample size: 9650 patients.

**STUDY POPULATION**

The main inclusion criteria are:

- history of coronary artery disease documented on a coronary angiography or by a previous myocardial infarction or a coronary revascularisation,
- 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 millimetres,
- sinus rhythm and resting heart rate equal to or higher than 60 beats per minute.

**STATE OF THE STUDY**

The recruitment phase has been completed with the inclusion of 10947 patients in 33 countries. In Italy, 269 patients have been randomized by 44 centers. Final results will be likely presented during the next ESC Congress in Munich.
Thrombus formation and platelet aggregation have a critical role in the pathophysiology of ACS. Therefore, therapies targeted at inhibition of the coagulation cascade and platelets are important, both in the initial medical stabilization and during subsequent revascularization. Randomized clinical trials (RCT’s) have demonstrated that antithrombotic therapies reduce the occurrence of ischemic events with an acceptable increase of the risk of bleedings. Unfortunately, hemorrhagic complications in the real world setting are more frequent than in RCT’s and such bleedings substantially increase both short- and long-term adverse outcomes and hospitalizations.

**STUDY OBJECTIVES**

The primary objective of the MANTRA Registry is to describe the clinical epidemiology of unselected patients with ACS, to evaluate their current management in Italy, and the related use of resources.

**STUDY DESIGN**

The MANTRA Registry is a prospective, multicentric, observational study of unselected ACS patients admitted to about 70 Coronary Care Units representative of the Italian network of Cardiology Centers.

**STUDY POPULATION AND METHODS**

All patients consecutively admitted in the participating CCUs during a 12 months period with a diagnosis of ACS (either STEMI or NSTEMI) with typical ischemic symptoms (occurring <24 hours prior to hospitalization), ECG changes suggesting ischemia and/or positive cardiac biomarkers, will be enrolled. Patients will be treated according to standard management strategies at enrolling sites. No specific treatment of the index ACS will be suggested during this observational study. However, caring physicians will be strongly invited to follow the current guidelines on ACS. In particular, early and careful risk stratification, timely reperfusion or revascularization, and appropriate antithrombotic therapy, when indicated, will be strongly encouraged. Patients will be followed-up for 6 months. Outpatients visits will be scheduled at 1 and at 6 months after the study entry.

Regional meetings with the participating cardiologists will be conducted with the aim to implement and discuss current international guidelines, results of recent studies in patients with ACS (both STEMI and NSTEMI) not yet included in official guidelines, local issues that can jeopardize the adoption of the most appropriate diagnostic/therapeutic strategies, the protocol of data collection in the registry.

**STUDY END-POINTS**

The study has the aim to describe the clinical epidemiology of patients with ACS admitted to a representative cohort of Italian CCUs. In addition, the implementation of the most recent guidelines on ACS will be assessed. Furthermore, the registry offers the opportunity to describe pharmacological treatments used during hospitalization, at discharge, and at 6 month follow-up visit. The study will particularly address the different antithrombotic strategies applied in ACS, their combination, and their safety profile. Finally, the utilization of invasive procedures and the incidence of the most relevant cardiovascular events and bleeding complications will be evaluated.

**SAFETY ANALYSIS**

Safety evaluation will include the description of serious adverse cardiovascular events and bleeding episodes, defined as follows:

- **Major bleeding.** Fatal bleeding; clinically overt bleeding associated with a fall of haemoglobin of 2 g/dl or more; clinically overt bleeding leading to transfusion of 2 or more units of whole blood or erythrocytes; bleeding in areas of special concern, such as intracranial, intra-spinal, intraocular, retroperitoneal, pericardial or a traumatic intra-articular bleeding.

- **Minor bleeding.** Minor bleeding causing permanent treatment cessation; other minor bleeding.

**STATISTICAL ANALYSIS**

All patients enrolled will be included in the analysis. Descriptive summaries will be presented either for all patients and different subgroups. Statistical tests may be carried out for exploratory purposes, as appropriate. Logistic regression models may be used to explore relationship between baseline co-variates and post-baseline end-points, as appropriate.

**STATE OF THE STUDY**

The protocol has been approved by the Ethical Committee of the study chairman. The expectation is to start patients’ enrolment in the last quarter of year 2008.
RATIONALE AND AIMS

The implementation of prevention strategies requires the activation of projects based on the identification of organizational models and on the definition of the role of Health System’s operators. The ANMCO - Prevention Working Group is developing a structured, operational project which defines the role of the hospital cardiology structures to ensure continuity of care between Hospital and outpatient Primary Care. The program is based on the organizational model, the Cardiology Office for Cardiovascular Prevention (CO-CP), designed to be activated throughout the whole national territory and also to form the Italian Network for Cardiovascular Prevention (IN-CP).

This Network’s tasks are:
- standardized patients’ record and follow-up
- global cardiovascular risk evaluation and management
- evaluation of CV incident events
- outcome research.

The coordinating center of the project is the ANMCO Research Center, Florence. Data are collected in the CO-CP by trained clinicians using an ad hoc software developed by the ANMCO-Prevention Working Group.

STUDY DESIGN

The RIACE trial, supported by the AIFA (Agenzia Italiana del Farmaco), is a multicentric, prospective observational study aimed to evaluate public health aspects in the field of cardiovascular prevention.

STUDY PROGRAM

The RIACE study is composed by 6 different, parallel and complementary parts aimed to describe the management of the global cardiovascular risk (see figure).

Part 1. Analysis of administrative databases of prescriptions, hospital discharge and survival status.

Part 2. Analysis of the database of general practitioners (GPs) (SIMG) containing clinical variables of about 300,000-400,000 patients collected by approximately 400 GPs.

Part 3. Epidemiology of the cardiovascular risk of a representative sample of patients followed by GPs in Italy. The aim is to prospectively describe the heterogeneity of the cardiovascular risk in a real world population.


Part 5. Avoidable cardiovascular events. The preventive strategies implemented before an acute coronary event will be described collecting data in nearly 1500 patients admitted in 40 hospital and academic CCUs.

Part 6. Prevention Programs of the Empoli area. A comprehensive program implemented in this area of Tuscany including 200,000 inhabitants followed by more than 180 GPs will be evaluated.
Il 5 per mille dell’IRPEF (sul mod. 730 o mod. UNICO PF o mod. CUD nel riquadro delle organizzazioni non lucrative) può essere donato con la tua firma e l’indicazione del Codice Fiscale 94070130482 per aiutare a sostenere Heart Care Foundation ONLUS.