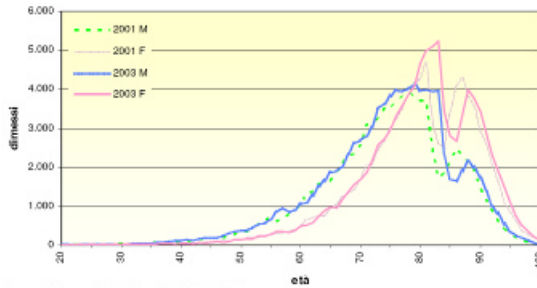


The clinical trial in CHIRON

The trial will consist in a randomized study whereby NYHA Class III patients are either provided or not with the home system using embedded technology to monitor them continuously.

Why Heart Failure and why CHF Class III patients

Heart failure affects 10 million Europeans and more than 22 million people worldwide and is expected to almost triple in 2020.



Fonte: Ministero della Salute – SDO 2001 e 2003

Congestive heart failure, is a condition that occurs when the heart is unable to pump enough blood to meet the needs of the body's tissues. Patients with CHF experience frequent and burdensome exacerbations of their condition, which requires admission to hospital for periods of more intensive treatment.

According to a study of the Heart of England Screening, one third of people with heart failure have dyspnoea which limits physical activity (occurring at rest, or upon minimal exertion – washing, dressing or walking from room to room) substantially and thus resulting in poor quality of life even relatively with the patients with other chronic conditions. It causes more severe impairment of physical functioning, social functioning and energy levels than chronic lung disease, arthritis, or other cardiac conditions such as angina.

Another symptom is weight gain when fluid builds up.

The reduced quality of life is reflected through significantly lower SF-36 scores¹ than those in the general population, with all eight areas of quality of life affected.

A method to assess CHF severity from the clinical point of view is by the New York Heart Association Classification (<http://www.hcoa.org/hcoacme/chf-cme/chf00070.htm>) which considers 4 classes.

- Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities.
- Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.
- Class III: marked limitation of any activity; the patient is comfortable only at rest.
- Class IV: any physical activity brings on discomfort and symptoms occur at rest.

The severity of the disease is linked with the age (see the graph referring to Italy and giving – split per age – the number of hospitalizations due to heart failure (years 2001 and 2003).

Congestive heart failure is the most common reason for hospitalization among the elderly. As the population ages the incidence of congestive heart failure is rising rapidly.

In UK the average length of stay for a patient admitted to hospital with heart failure is over 13 days, three times the average length of stay for all patients and about 1,000,000 days of inpatient care (2% of all inpatient bed days in England).

Similar data are valid also for Italy (10 days as average in 2001) and for other European countries.

Mortality in CHF is related to the severity of the disease, in turn related to the severity of left ventricular dysfunction (which might be assessed by left ventricular ejection fraction by imaging techniques, also relatively non-invasively).

¹ Short Form (36) Health Survey (<http://www.sf-36.org>); The SF-36 consists of eight scaled scores, which are the sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The eight sections are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health.

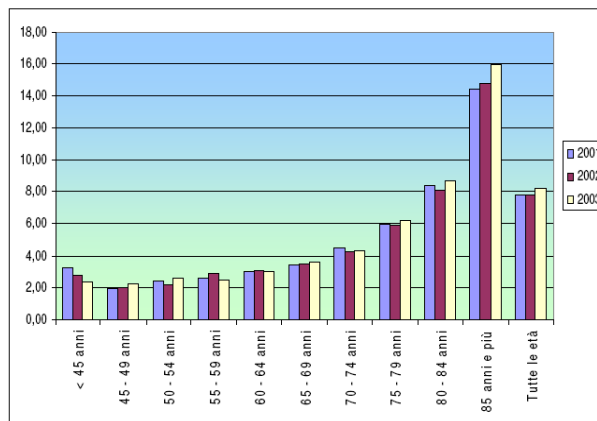
According to the statistics, the percentage of mortality for all the CHF patients ranges from 2% to 16% depending on the age and severity of congestive heart failure (as assessed by codes of the International Classification of Diseases: ICD-9-CM 428.x).

The graph – referring to Italy – shows the mortality rate of CHF patients according to the age (data are related to 2001 and 2003).

If one concentrates on class III a higher proportion of death (>40%) might be anticipated in 12 months, particularly in the elderly.

According to the available data, 60% of all deaths are due to chronic diseases², and within these chronic diseases, cardiovascular diseases represent the most common cause of death in Europe³. It is mandatory to provide novel solutions to avoid the increase of deaths from chronic diseases foreseen over the next 10 years.

Although chronic diseases expense is estimated to over 70% of healthcare burden, chronic diseases are not yet managed appropriately. **Computer assisted treatment and monitoring** will provide a solution to support more personalized and disease-oriented healthcare for life-long independent living and integration across the healthcare chain, without a considerable increase in costs.



Fonte Ministero della Salute – SDO 2001-2003

Lack of clinical assessments of remote monitoring

There are no trials of remote monitoring (RM) for chronic disease conditions with rigorous HTA outcomes.⁴

In the specific case of heart failure it seems that there is a consensus in the medical community that early detection of the degeneration of the patient's condition is an absolute clinical necessity to deliver high-quality healthcare service to the population; in fact clinical interventions early in the deterioration phase could prevent hospitalization if mechanisms are in place to define onset and effect

therapy change.

Currently remote monitoring in heart disease is done by implanted technologies that monitor disease condition and telemeter their recorded data for assessment by clinicians using bespoke information technology.

There is no doubt that a particular Remote Monitoring advantage is the availability of continuous rather than sporadic data to enhance understanding of the dynamic disease state. As an example, daily measurements of IPI (Intrathoracic Pulmonary Impedance) have been predictive of heart failure decompensation and atrial and ventricular arrhythmogenesis, but with variable relationships between daily changes and other measures of heart failure.

Nevertheless the outcomes of the studies available on remote monitoring are often contradictory and not so clear. An analysis done in UK on 4264 heart failure remote contact (RC) through external telemonitoring (ETM)/ transfer of physiological data (weight, BP, ECG, heart rate) by phone or digital link and by structured telephone support (TS) showed a reduction of all causes of mortality by an average of 20% and a reduction of hospital admission due to heart failure by 21 %. However other recent studies (HOME-HF and HHH Study) showed no reduction in death or hospitalization even if emergency unplanned hospitalisations were reduced substantially.

² WHO report, 2006, Building foundations for eHealth

³ Allender S., Scarborough P., Peto V., Rayner M, Leal J., Luengo-Fernandez R., Gray A., **European cardiovascular disease statistics** (2008).

⁴ The HTA (Health Technology Assessment) programme produces independent research about the effectiveness of different healthcare treatments and tests for those who use, manage and provide care in the National Health System

Furthermore studies on the effect of Remote Monitoring in the Quality of Life are very limited.

We conclude that optimal care pathways/clinical application for RM technologies are not defined and their definitions are crucial for best patient care/experience and realisation of best value of the technology for the healthcare system.

How the CHIRON trial will be organized

Two groups of patients (a group using the CHIRON solution and the second one with similar health problems but treated in the conventional way) will be involved on a voluntary basis.

The patients will be located in Italy (selected by the Policlinico Umberto I in Rome) and in UK (Southampton University Hospitals NHS Trust). The trials will have a length of 1 year (the last year of the Project).

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Remotely monitored parameters will be selected among:

- Weight (fluid retention),
- ECG
- breathing rate variability,
- blood pressure variability,
- Blood constituents (Na⁺, K⁺, BNP, CO₂ and O₂ tension, CRP inflammatory marker, Hemoglobin, alcohol content – this is a growing concern in UK),
- intrathoracic pulmonary impedance (IPI),
- nocturnal apnoea and sleep apnoea,
- other aspects such as Diet (drink), Gym (activity index).

During the hospital checks, imaging examination will be executed (tissue characterization to detect ischemic episodes).

For patients living in pairs, the wife or husband of the patient will play an important role; part of the activity will be devoted also to train them on how to support the patients and how to collaborate during the overall phase of the Project verification.

Metrics

The metric for the performance will be the number of further hospitalization days in the 12-month follow-up (primary end-point for CHIRON). Mortality in 5 years is a secondary end-point in CHIRON, yet a primary one for a study that A POSTERIORI will also compare the simpler measures with the more complex and numerous ones of the integrated tissue analysis as well.

We will use also questionnaires on Quality-of-Life filled in by the patients at the beginning, during and at the end of the trial.