

# The T.O.S.CA. Project: Research, Education and Care

## *Il Progetto T.O.S.CA.: Ricerca, Formazione e Cura*

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On behalf of T.O.S.CA. investigators

**ABSTRACT:** *The T.O.S.CA. Project: Research, Education and Care. E. Bossone, G. Limongelli, G. Malizia, F. Ferrara, O. Vriz, R. Citro, A.M. Marra, M. Arcopinto, E. Bobbio, D. Sirico, L. Caliendo, A. Ballotta, A. D'Andrea, A. Frigiola, J. Isgaard, L. Saccà and A. Cittadini. On behalf of T.O.S.CA. investigators.*

Despite recent and exponential improvements in diagnostic-therapeutic pathways, an existing "GAP" has been revealed between the "real world care" and the "optimal care" of patients with chronic heart failure (CHF). We present the

T.O.S.CA. Project (Trattamento Ormonale dello Scompenso Cardiaco), an Italian multicenter initiative involving different health care professionals and services aiming to explore the CHF "metabolic pathophysiological model" and to improve the quality of care of HF patients through research and continuing medical education.

*Keywords: heart failure, metabolic pathophysiological model, quality of care, TOSCA.*

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## Introduction

Chronic Heart Failure (CHF) is a growing public health problem impacting heavily on patient survival, quality of life and healthcare costs. Due mainly to coronary artery disease [1], hypertension, valve disease and cardiomyopathies, it is characterized by (a) shortness of breath at rest or during exertion, and fatigue; (b) signs of fluid retention such as pulmonary congestion or ankle swelling; (c) and an objective evidence of an abnormality of the structure or function of the heart at rest [2].

The incidence and prevalence (2-3%; 10-20% after 75 years of age) are clearly increasing in industrialized countries [2, 3]. According to the European Society of Cardiology roughly 15 million patients were diagnosed with CHF out of a population of 900 million people.

However, despite considerable investment in research and guidelines dissemination by several scientific societies, the treatment gap of CHF continues to widen between evidence-based approach and practice reality across the continuum of care, resulting in an

unsustainable high morbidity and mortality along with an increasing economic and social burden [4-8].

We herein present the design and the aims of The T.O.S.CA. Project (Trattamento Ormonale dello Scompenso Cardiaco): an Italian multicenter initiative aiming to explore the CHF "metabolic pathophysiological model" and to improve the quality of care through the implementation of a dedicated continuing medical educational program.

## Research

Despite different hypotheses, no single pathophysiological paradigm of CHF has been definitively established. One logical explanation of the inability to define the syndrome of CHF in precise mechanistic models is that the clinical syndrome of CHF almost certainly represents the summation of multiple anatomic, functional, and biological alterations that interact together in a complex way. Thus, it is not surprising that investigators employing simple models in an attempt to describe the syndrome of HF have failed [9].

Nowadays, the most accepted hypothesis explaining CHF pathophysiology and its progression is the “neurohormonal model”. According to this paradigm, heart failure progresses as a result of the overexpression of biologically active molecules that exert toxic effects on the heart and circulation. A variety of molecules including norepinephrine, angiotensin II, endothelin, aldosterone, and tumor necrosis factor have been implicated as some of the factors that contribute to disease progression in the failing heart [9].

The evidence in support of this point of view is derived from many experimental and clinical studies showing that overexpression of active molecules reported above can contribute to disease progression independently of the hemodynamic status of the patient and that antagonizing neurohormones improve clinical outcomes of patients with CHF. Indeed, the “neurohormonal axis” is the main target of medical treatments proved to be efficacious in CHF, such as ACE-I, beta blockers and spironolacton/eplerenon [10].

However, the “neurohormonal model” displayed several pitfalls. A complete inhibition of hormonal axes involved in CHF progression is difficult to obtain for dose-limiting effects of drugs and also for alternative metabolic pathways that are not antagonized by conventional therapy. On the other hand, other unknown molecular interactions potentially involved in the progression of CHF are likely to be involved.

Despite the effectiveness of the neurohormonal model to explain disease progression and the many insights that it provided for the development of new therapies, there is an increasing clinical evidence that suggests that our current models fail to completely explain disease progression.

The observation that the survival curves become parallel following neurohormonal antagonism suggests that there may be an attenuation or loss of effectiveness of neurohormonal antagonism as heart failure progresses. Thus, neurohormonal models may be necessary but not sufficient to explain all the aspects of disease progression of the failing heart.

Based on these observations and on the poor prognosis despite optimal therapies, alternative mechanisms that contribute to CHF progression are being actively explored. In this regard, recent evidence suggests that a metabolic imbalance occurs in CHF, characterized by a predominance of the catabolic status over anabolic drive. The most impressive example is seen in end-stage CHF known as “cardiac cachexia” characterized by sustained weight loss, particularly lean mass, and rapid deterioration of clinical conditions, attributed to a prevalence of catabolic pathways. Whether such hormonal imbalance is a mere epiphenomenon or an important pathophysiological mechanism in CHF progression is still matter of debate. The main evidence concerning anabolic deficiencies in CHF patients is described in a recent study by Jankowska *et al.* [11]; specifically, deficit of each anabolic axis (adrenal, gonadal and somatotrophic axes) represents an independent marker of poor outcome in CHF patients and the coexistence of more than one deficiency identifies a subgroup of patients with a higher mortality.

The most involved hormonal axes include growth hormone (GH), its tissue effector insulin-like growth factor-1 (IGF-1), thyroid hormone, insulin and anabolic steroids. Taken together, these alterations could be recognised as a multiple hormonal and metabolic deficiency syndrome (MHD) in HF patients. MHD bears a significant impact on cardiac performance and HF progression [12].

These considerations provide novel and interesting opportunities including: (a) The identification of new prognostic markers; (b) The implementation of knowledge about multiple hormonal deficiency syndrome (MHD); (c) The basis for new therapeutic approaches in this regards our group has some recent experiences in GH replacement therapy.

Chief among the hormonal systems the GH/IGF-1 axis play a pivotal role, being the most powerful anabolic pathway in the human body. In fact, GH and IGF-1 are essential for preserving both cardiac morphology and performance in adult life. The finding of low IGF-1 levels in CHF patients is relevant for many reasons. First, individuals with low IGF-1 levels undergo cardiovascular alterations that are corrected by replacement therapy; in this regards our group has some recent experiences in GH replacement therapy [13]. Second, large population-based studies show that a low level of IGF-1 is predictive of HF. Finally, low IGF-1 levels are associated with reduced skeletal muscle performance and endothelial dysfunction [14].

Thus, study of GH/IGF-1 axis represents the main topic of T.O.S.CA. investigations.

Preliminary insights from T.O.S.CA. project about clinical status and cardiovascular performance in patients with low IGF-1 levels were presented at the recent European Congress of Cardiology [15].

#### ***Aims of T.O.S.CA. Project - Research:***

The T.O.S.CA. project therefore represents a unique opportunity to create a large database from several centers both in Italy and abroad in order to respond to some fundamental pathophysiological questions. First, what are the reference values of the main anabolic axes in a large Italian CHF population, coming from different regions of our country? What is the actual prevalence of multiple hormone deficiencies in CHF? Second, we will evaluate whether anabolic deficiencies identify subgroups of CHF patients with worse clinical status and more impaired LV architecture, function and cardiopulmonary performance. Third and more importantly, we will be able to address the question of whether single or multiple hormone deficiencies affect heart failure progression and poor outcome.

Smaller case-control studies will address more specific topics such as the relation between direct assessment of myocardial ultrastructure and gene expression profile, and the anabolic/catabolic balance, evaluating myocardial biopsies of CHF patients undergoing cardiac surgery.

#### **Education**

Despite the recent and exponential improvements in diagnostic-therapeutic pathways, an existing “GAP” has been revealed from the “real world

care” and the “optimal care” of patients with CHF [16-28]. A recent Italian multicentric population-based study has confirmed the “GAP” in health status among socioeconomic groups particularly evident for CHF characterized by an excess of unnecessary hospitalization [29].

In Italy the educational health program (defined as E.C.M: Continuing Medical Education) consists of theoretical and practical activities promoted by agencies and scientific societies and regulated by specific legislation (DLgs 229/99 and L. 238/00). In particular, the purpose of the T.O.SCA project educational branch is to improve the quality of care of CHF patients (timeliness, efficiency and effectiveness) in different clinical settings. It consists of a specialized E.C.M.-meta-model designed by a dedicated multidisciplinary team and applied through an intensive three phases educational year (Fig. 1).

**Phase 1: Pre-T.O.SCA:** (a) Selection of participant hospitals and investigators; (b) Investigators’ training (meeting-tutorial-web site); (c) Presentation and beginning of the project; (d) Analysis “status quo” of actual diagnostic-therapeutic pathways. Data (i.e. medical history, symptoms and signs, electrocardiographic, chest X Ray, echo-Doppler and other imaging results, in-hospital treatment disposition, follow-up) will be collected on a standard case-report form and then forwarded to the T.O.SCA. registry coordinating center for analysis. Quality of care

is going to be assessed by measuring the use of “key indicators” as for current ESC guidelines.

**Phase 2: T.O.SCA Implementation:** (e) Improvement of adherence to the guidelines through dedicated tools;(f) Weekly-monthly meeting (ECM) and quality control.

**Phase 3: post-T.O.SCA:** (g) Analysis post guidelines implementation. (h) Presentation and discussion of results.

### Care

The actual picture of CHF in Europe and Italy is predominantly represented by continuous acute hospital admissions, poor prognosis, an ongoing drain of health care expenditure and discomfort for the patients and care givers [30-33]. Thus, in order to optimize the medical management, reduce the hospitalization and readmission rate, improve and maintain optimum quality of life, and balance the cost/benefits ratio, the European Society of Cardiology guidelines recommend the implementation of structured multidisciplinary CHF disease-management program (Class of recommendation I, level of evidence A) taking into account patient needs, financial resources, available personnel, and administrative policies [2]. In this regard the T.O.SCA. team has developed a meta-model of structured CHFMG (Chronic Heart Failure Management Program) (Fig. 2) on the area

of Amalfi Coast in Southern Italy as a continuum between the community hospitals and the territorial health system serving 110.000 habitants among 13 cities. The CHF out-patient clinic represents the platform of the Amalfi Coast CHFMG, directed by clinical cardiologist and coordinated by registered nurse, along with multidisciplinary team. Patient-first contact with CHFMG may be during hospitalization or as specific request from primary care physician. During the first outpatient visit the cardiologist will assess the clinical status and current therapy, design an effective follow-up strategy such as ambulatory care, day service, day hospital [35-37]. A tertiary level hospital constitutes the referral center for invasive and surgical treatments (revascularization procedures, valvular and ventricular surgery, cardiac resynchronization therapy, implantable cardioverter defibrillator, heart transplantation and ventricular assist devices). Cardiac rehabilitation and genetic counseling are also provided when indicated.

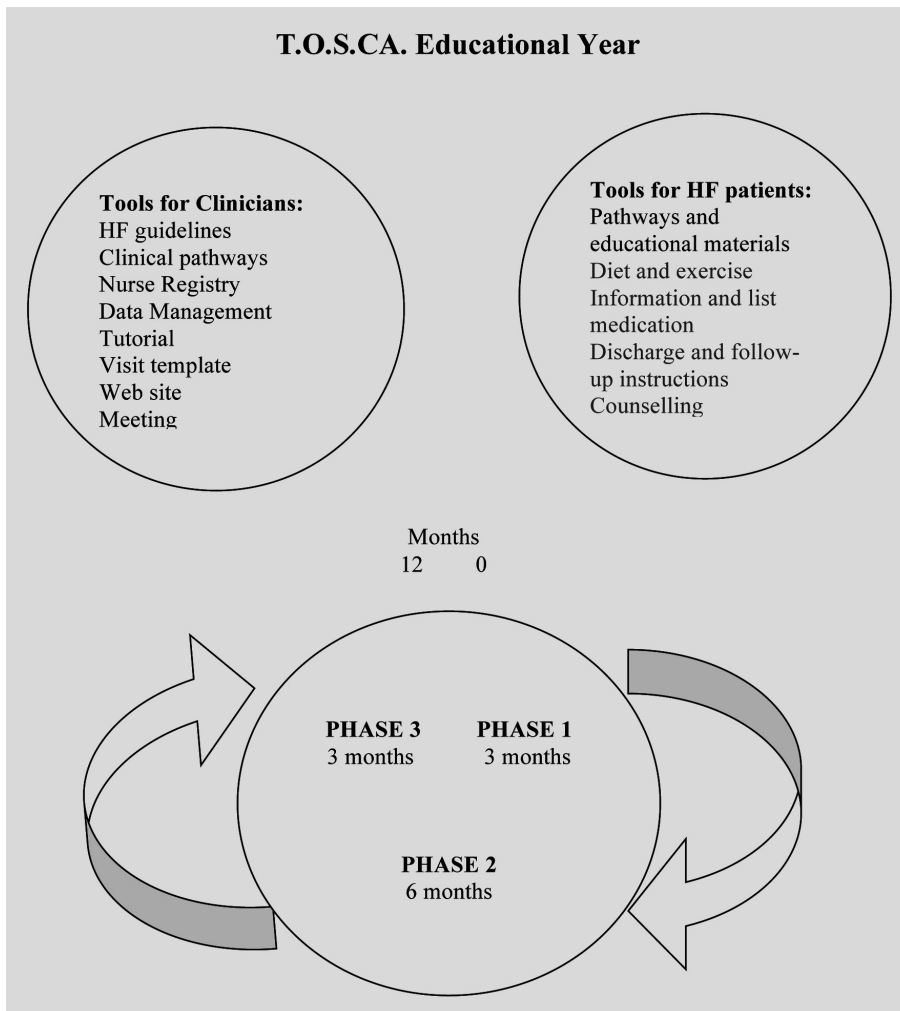


Figure 1.





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## Appendix

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