Introduction

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Starting any article, even only an introductory one, on heart failure by reporting epidemiological data to express the size of the problem is such a widespread habit as to be definitely inadvisable. Nevertheless, since recent official data on the clinical epidemiology of heart failure in the United States have been made available it seems reasonable to have a glance at them[1,2]. In brief, after the number of hospital admissions with a primary diagnosis of heart failure had increased from 377 000 in 1979 to 978 000 in 1998[3] (2.5 million admissions with a primary or secondary diagnosis of heart failure), today 4.8 million Americans (roughly 1% of the population) have heart failure. Each year 550 000 new cases are diagnosed and over 200 000 deaths are recorded as being due to heart failure. More than 6.5 million days are spent in hospital each year, costing about 20 billion dollars and exceeding 10% of the overall expenditure for cardiovascular diseases. American data collected from the community[3-5], just as our data from the TEMISTOCLE study[6], indicate that in between 30 to 60% of cases patients are readmitted within 3-6 months of discharge. Thus, the time spent dealing with heart failure is not time wasted.

In the last 20 years scientific and clinical interest in heart failure has flourished, in part because of the growing awareness of the increasing size of the problem and, in part, in relation to the greater availability of investigative strategies and therapeutic possibilities. The interest of researchers and clinicians has, however, been almost totally concentrated on chronic heart failure. Even the guidelines[7], scanty and terse on the subject of acute heart failure, bear witness to this. In fact, despite the huge progress in other areas of cardiology, the therapeutic approach to acute heart failure is essentially the same as that of 30 years ago[8].

There are numerous reasons why interest in acute heart failure is limited[9]. These include: 1) the heterogeneity of the patients and the imprecise definition of the clinical problem, 2) the undefined aims of treatment, particularly whether directed to hemodynamic endpoints, to a short term reduction in symptoms, or to the reduction of major clinical events in the short term and mid term, 3) the difficulty in standardizing methodology in a type of research dealing with very severe, rapidly evolving, clinical situations, 4) for the same reason, the paucity of clinical trials, which include limited numbers of patients and are usually of mediocre quality, and finally 5) the scarcity of stimulating new pathophysiological and therapeutic ideas.

The first point, an unequivocal definition, could seem academic, but does in fact have a fundamental clinical and scientific importance. As long as we do not exactly know what we are talking about, we cannot understand each other and carried out experiences cannot be generalized. Two clinical classifications were recently proposed for acute heart failure, both having the advantage of clinical practicality and simplicity[9-11]. Table I and figure 1 summarize these two classifications. The classification proposed by Stevenson et al.[10,11] predominantly concerns patients with worsened chronic heart failure rather than patients with an acute *de novo* episode of heart failure according to the classification proposed by Felker et al.[9]. Felker's classification is less pathophysiological, more descriptive, but it can be clinically useful. One aspect that clearly emerges from any attempted classification is the lack of a specific meaning of the term acute heart failure, which acts as an umbrella term for various situations requiring different therapeutic approaches. One "local" aspect of the classification concerns the Italian term of

Table I. Decompensated heart failure. Classification according to Felker et al.[9].

Decompensated heart failure: new or worsening symptoms/signs of dyspnea, fatigue, or edema leading to hospitalization or unscheduled medical care.

Acute heart failure: sudden onset of symptoms or signs of heart failure in a patient with no history of heart failure and with a previously normal cardiac function.

Exacerbation of heart failure: increasing signs or symptoms of heart failure after a period of relative stability in a patient with an established diagnosis of heart failure.

Acute pulmonary edema: an acute increase in the pulmonary interstitial and airspace water, characterized by the sudden onset of severe dyspnea and by signs of pulmonary congestion.
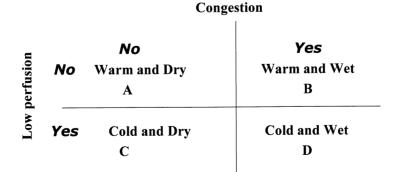
scompenso cardiaco ("cardiac decompensation") which is generally used as the analogue of heart failure. Actually, heart failure would be better described as *insufficienza cardiaca*, a clinical situation which may be compensated or decompensated. Only in the latter case would the term *scompenso cardiaco*, analogous to the term decompensated heart failure, be appropriate.

According to Stevenson's classification[10,11], acute pulmonary edema is a specific clinical situation in which the patient is "wet" and may be "warm" or "cold". It may either be acute heart failure or an exacerbation of heart failure according to Felker et al.[9]. Some clinical situations are clear: acute heart failure may be precipitated by myocardial ischemia or myocardial infarction with or without its mechanical complications, and precariously compensated chronic heart failure may be exacerbated by uncontrolled arterial hypertension, cardiac arrhythmias, infections or other minor triggering factors. However, in many instances the direct cause of acute pulmonary edema remains hypothetical. As for the therapy, the literature is particularly lacking in controlled, randomized trials on this subject.

Given the emerging clinical and epidemiological relevance of heart failure with a preserved ventricular systolic function, the observation that this clinical pattern may also occur in the setting of acute pulmonary edema is particularly important[12]. This is normally an exacerbation of chronic heart failure characterized by marked arterial hypertension in subjects with non-dilated or not markedly dilated, hypertrophic ventricles, in which the fundamental defect is a diastolic dysfunction with a reduced ventricular relaxation and compliance. In these patients a moderate volume overload may give rise to a marked increase in ventricular pressure because of the inability of the heart chambers to adapt, leading to an acute increase in pulmonary interstitial and airspace water. The same can occur because of a sharp increase in the resistance to ventricular ejection related to an elevation in vascular resistances. Obviously myocardial ischemia can play a relevant role in causing or worsening diastolic dysfunction. These pathogenetic characteristics explain the relative speed with which acute pulmonary edema favorably responds to diuretics and vasodilators.

The prognostic stratification of any type of unstable heart failure, acute or exacerbated, is likewise poorly defined. Table II reports some variables found to be independent predictors of outcome in multivariate analysis in two recent trials, OPTIME-CHF[13] and FIRST[14]. Nothing very new was revealed. It is possible that more interesting elements will emerge from ongoing studies of markers such as brain natriuretic peptide[15-17] and troponin[18].

The articles contained in this Supplement of the *Italian Heart Journal* deal with the problem of the overall approach to the management of acute exacerbations of heart failure. Acute heart failure as defined by Felker et al.[9] is not specifically taken into consideration. The analysis of the acute treatment is privileged, albeit in the context of a comprehensive picture of the treatment of the exacerbations of chronic heart failure (Ghio et al.). The problem of inotrope therapy in heart failure is also

Congestion

		No **Warm and Dry** A	**Yes** **Warm and Wet** B
Low perfusion	**No**	Warm and Dry / A	Warm and Wet / B
	Yes	Cold and Dry / C	Cold and Wet / D

Figure 1. *Decompensated heart failure classification according to Stevenson et al.[10]. The classification is based on the clinical identification of four hemodynamic profiles related to the presence or absence of elevated ventricular filling pressures (wet and dry) and tissue perfusion that is adequate or critically limited (warm and cold). The identification of elevated filling pressures mainly relies on the symptoms of orthopnea and the finding of an elevated jugular venous pressure, estimated by measuring the vertical distance from the top of the jugular pulsation down to the sternal angle. The identification of peripheral underperfusion relies on a low pulse pressure (a proportional pulse pressure < 25%) and on the cold temperature of the forearms and legs. According to these criteria, four clinical-hemodynamic profiles can be identified: A - warm (adequate peripheral perfusion) and dry (no congestion), B - warm (adequate peripheral perfusion) and wet (congestion), C - cold (inadequate peripheral perfusion) and dry (no congestion), D - cold (inadequate peripheral perfusion) and wet (congestion).*

Table II. Independent predictors of mortality after hospitalization for decompensated heart failure.

	Hazard ratio	p
OPTIME-CHF[13] (n=949)		
Age (per 10 years)	1.27	0.01
NYHA class (IV vs other)	1.94	0.004
Systolic blood pressure (per 10 mmHg)	0.78	0.0004
Blood urea nitrogen (per 5 mg/dl)	1.33	< 0.0001
Serum sodium (per 5 mmol/l)	0.75	0.018
FIRST[14] (n=471)		
Age (years)	1.016	0.053
Sex (male)	1.853	0.0014
Randomized to epoprostenol	1.534	0.0049
NYHA class (IV vs other)	1.579	0.0170
Dobutamine use at randomization	2.189	0.001

examined (Campana et al.). This is perhaps the most disappointing aspect of the therapy-oriented clinical research in cardiology in the last few decades. One wonders why; Rapezzi et al. try to respond. The recent clinical availability of a new class of drugs, the calcium sensitizers, has reopened the game. In reality, the first move was not a good one: pimobendan, the first calcium-sensitizing drug tested in a mortality-morbidity trial (PICO) did not yield favorable results[19]. However, together with its calcium-sensitizing action, pimobendan also has a phosphodiesterase-inhibiting action, thus resembling other inodilators (milrinone, etc.) of demonstrated inefficacy or worse. Levosimendan has a pure calcium-sensitizing action (it inhibits phosphodiesterase III at doses much higher than those used clinically) and has, finally, allowed some favorable clinical results to be seen in randomized controlled trials against placebo. This has rekindled hopes. With regard to this, Erhardt reports the fundamental characteristics of the drug and its mechanism of action. Follath and Nieminen et al., who coordinated the main clinical research conducted with the drug, summarize and discuss its effects. Spargias et al. report on a preliminary experience on the repetitive administration of levosimendan in patients with end-stage heart failure. But the clinical problem of acute or exacerbated heart failure is not confined to cardiologists and internists. It is also a problem for non-cardiac intensive care specialists. In this respect, Braschi and colleagues analyze the overall approach to a surgical patient with severe, unstable heart failure, in a more complex setting and with more etiological factors than normally encountered by the cardiologist. In the same context Mebazaa and colleagues, who have the greatest international experience of the clinical evaluation of levosimendan in the field of anesthesia and intensive care, report some of their data.

Overall levosimendan seems to be effective and, importantly, reasonably safe. The multitude of drugs tested in heart failure and discarded after disappointing morbidity-mortality trials failed not because they were ineffective but because they were unsafe. Safety is of paramount importance in a multiorgan syndrome such

as heart failure, with a profoundly altered biological *milieu*. This is particularly so in the unstable stages of the disease. Any drug given in such a situation requires careful monitoring and competent management. The available experiences are consistent in depicting levosimendan as a safe drug if such requirements are met.

Levosimendan has recently been authorized for clinical use even in Italy. We will set about incorporating it into our clinical practice. This Supplement of the *Italian Heart Journal* is intended to be an instrument to use it as profitably as possible.

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