Results of prospective multicenter study on heart failure on Campania Internal Medicine wards: the FASHION study

Fernando Gallucci,[1] Ilaria Ronga,[1] Andrea Fontanella,[2] Generoso Uomo[1] and the FASHION Study Group

[1]Internal Medicine Unit 3, Cardarelli Hospital, Napoli; [2]Internal Medicine Unit, Fatebenefratelli Hospital, Napoli, Italy

ABSTRACT

Heart failure (HF) is characterized by a high prevalence and hospitalization rate with considerable health and social impact; the knowledge of its epidemiological features remains the mainstay to assess adequacy of the health care needs. The aim of this study was to evaluate the prevalence of HF in Internal Medicine Units of the Campania region (Italy) and patients' characteristics. We recruited all patients with HF admitted between April 1 and June 30, 2014, in 23 Units of Internal Medicine: 975 patients (19.5% of 5000 admissions), 518 women and 457 men, mean age 76.9±9.9 (range 34-100) with 741 (76%) older than 70 years. The mean age was higher in women than men; 35.8% of patients had atrial fibrillation, with higher prevalence in women than in men. Coronary artery disease represented the leading etiology while prevalence of non-ischemic heart failure was higher in women. New York Heart Association class was indicated in 926 patients. Left ventricular ejection fraction (LVEF) was measured in 503 patients; 18.4% of patients had a severely reduced LVEF<35%, mostly men (P=0.0001) and 67.4% presented a LVEF>40%. At least one hospital admission in the previous 12 months was registered in 39.6% of patients. One, two and more than two relevant comorbidities were present in 8.6%, 24.7% and 64.8% of patients, respectively. Arterial hypertension and coronary artery disease were more frequent in female. In conclusion, advanced age and clinical complexity were the main characteristics of HF patients hospitalized in the Internal Medicine Units in Campania. Gender differences also emerged from the analysis of demographic parameters and etiopathogenetic features. Some diagnostic and therapeutic aspects not in line with that recommended by the most recent HF international guidelines were registered.

Correspondence: Fernando Gallucci, Internal Medicine Unit 3, Cardarelli Hospital, via Cardarelli 9, 80131 Napoli, Italy. Tel.: +39.081.7472102 - Fax: +39.081.7472104.
E-mail: fernandogallucci@libero.it

Key words: Heart failure; internal medicine wards; epidemiology; gender difference; aging.

Conflict of interest: the authors declare no potential conflict of interest.

Members of the FASHION (*FA*DOI *S*tudy On *H*eart Fa*i*lure *On* Campania Internal Medicine) Study Group
Abete P, Ambrosca C, Avella F, Beneduce F, Boni R, Borgia M, Cannavale A, Caputo D, Caserta L, Caso P, Ciaramella F, Cositore G, Dalia C, De Donato MT, De Feo V, Esposito N, Fimiani B, Galderisi M, Giaquinto E, Giordano P, Grasso E, Guida L, Ilardi A, Maffettone A, Mastrobuoni C, Mayer MC, Rabitti PG, Ranucci R, Renis M, Schiavo A, Tassinario S, Zuccoli A.

Received for publication: 15 February 2016.
Revision received: 27 September 2016.
Accepted for publication: 21 October 2016.

Italian Journal of Medicine 2017; 11:184-190
doi:10.4081/itjm.2017.705

Introduction

Heart failure (HF) is a global pandemic affecting an estimated 26 million people worldwide and resulting in more than one million hospitalizations annually in both the United States and Europe.[1,2] Nowadays HF is the leading cause of hospitalization and mortality, reaching 40% within five years following hospitalization.[3] Survival estimates are 50% and 10% at 5 and 10 years after the diagnosis, respectively.[4-6] In addiction, patients with HF are at high risk of repeated hospitalization, with a readmission rate of 25% of patients within 30 days from index hospitalization.[7] Estimates of the prevalence of symptomatic HF in the general European population is similar to that in the United States, and ranges from 0.4% to 2%[8] while the overall prevalence ranges from 1% to 12%.[9] Despite recent advances in clinical approach, diagnosis and therapeutic management, the incidence and prevalence of HF are still increasing, owing to the better control of the disease and, largely, to the aging of the population.[10] Due to the longer life expectancy, relative incidence of HF in women is approaching the one-half of HF cases.[11]

In Italy, it is estimated that 2% of the population is affected by HF, reaching the number of about 1,000,000 inhabitants (435,000 persons older than 65 years of age and 120,000 older than 80).[12] HF is the leading cause of hospitalization over 65, thus it remains a growing public

health problem. In the year 2012, the number of hospitalization for HF was around 200,000 events over a number of near 1,000,000 admissions for cardiovascular diseases, with an average length of stay of 9.1 days.[13] Considering specifically the Campania region, the rate of hospitalization because of HF was of 343.3/100,000 inhabitants, representing the leading cause of hospitalization in subjects over 65 years old (1369/100,000 inhabitants).[14,15] It is relatively common that patients admitted to hospital for any cause may suffer from HF as a coexisting medical problem, establishing a strong network of chronic diseases closely interrelated that greatly complicates diagnosis, management and outcome.[16] As a consequence the HF is no longer considered as an isolated syndrome but part of a larger framework of multi-morbidity requiring a holistic approach in order to improve prognosis and quality of life.

The awareness of the epidemiological realities is a necessary datum for assessing the adequacy of *local* management but the available data on HF are not univocal, especially for the heterogeneity of the populations from which they are detected and managed [territory, Cardiology and Internal Medicine (IM) Units, and so on].[17]

The aim of this study was to evaluate the prevalence, clinical profile and relevance of comorbidities, the routine diagnostic and therapeutic work-up of chronic HF and to assess age and gender-related differences of the disease in patients coming from Campania region, admitted to IM Units.

Materials and Methods

The present study is a prospective, multicenter, observational study performed in 23 Internal Medicine wards representative of the regional setting of Campania. Diagnosis of HF was based on the guidelines of the European Society of Cardiology (ESC) 2012.[18] For each patient the following data were collected at admission and recorded on an electronic format to allow assessment of provider-related differences in the clinical profile of the study population: day of hospitalization, gender, age, heart rate and rhythm, blood pressure, etiology of HF, New York Heart Association (NYHA) class, ejection fraction by echocardiography, previous hospitalizations up to twelve months before, comorbidities (see below), drug treatment including the use of new anticoagulant agents. Comorbidity was defined as the presence of at least one of the following: chronic obstructive pulmonary disease (COPD), diabetes mellitus, arterial hypertension, renal dysfunction, coronary artery disease, cerebral vascular diseases, liver diseases, malignancies. Measurement of left ventricular ejection fraction (LVEF) was used to estimate LV function. A LVEF >50% indicated preserved systolic function, as indicated in HF ESC guidelines.[18]

Statistical analysis

Continuous variables were summarized with mean and standard deviations and categorical percentages. Discrete variables were calculated by frequency percent and compared by the chi-square test. A P value <0.05 was considered as statistically significant. Statistical analysis was carried out by using SAS software (version 9.1; SAS Institute, Cary, NC, USA).

Results

Nine hundred seventy-five patients admitted to IM wards with HF (19.5% of 5000 total admissions) between April 1 to June 30, 2014, were enrolled; 518 females (53%) and 457 males (47%). The baseline demographic and clinical features of studied patients are summarized in Table 1. Patients aged older than 70 were 741 (76%). Mean age [±standard deviation (SD)] was 76.9±9.9 (range 34-100). The mean age was higher in women than men, 79.3±9.0 *versus* 74.36±10.3 (P<0.05). Three hundred forty-nine patients (35.8%) had atrial fibrillation, with higher prevalence in women (41% *vs* 33.9%; P=0.02). With regard to underlying etiology of HF, coronary artery disease remained the leading cause without difference between men (62.3%) and women (52.5%); otherwise, the prevalence of non-ischemic heart failure resulted higher in women (47.4% *vs* 37.6%; P=0.002). NYHA class was indicated in 926 (94.9%) patient without significant gender difference observed in each subclass. 503 (51.5%) patients had LVEF measurement at the initial evaluation for enrollment; 170 patients (33.7%) presented with LVEF <40% without significant gender difference. Ninety-three patients (18.4%) had a severely reduced LVEF (<35%; 60 men and 33 women; P=0.0001); 87 patients (17.2%) presented with LVEF>50% with a higher prevalence of women (20.8% *vs* 13.7%; P<0.05). Three hundred eighty-seven patients (39.6%) had almost one hospital admission in the previous twelve months.

At the time of hospital admission, 8.6% of patients had one known disease other than HF, 24.7% had two comorbidities, and 64.8% more than two comorbidities (Figure 1). Arterial hypertension was present in 76.9% of patients with HF, with a significant higher prevalence in women (81.5%) than in men (71.8%), P=0.0001). Congestive heart failure (CHF) and COPD frequently coexist (49.4% of patients), with a significant gender-related difference (44.2% females *vs* 58.8% males - P<0.0001). Diabetes was found in 42% of patients. Chronic kidney disease (CKD) was present in 348 patients (35.7%), with higher prevalence in women (37.3% *vs* 33.9% - P=0.005). The most prescribed drugs were: β-blockers, angiotensin converting

enzyme (ACE)-inhibitors and furosemide (Table 2). Out of the 170 patients with LVEF <40%, 120 (70.6%) received β-blockers. Interestingly, β-blockers were also used in 248 of the 482 (51.5%) patients with COPD, with a significantly higher frequency in men (139 *vs* 109, P=0.003). ACE-inhibitors were registered, in addition to a β-blocker, for all patients with EF <40% and in 172 of 348 (49.4%) patients with renal insufficiency. Loop diuretics were taken by 705 patients (72.3%) to control fluid retention and relieve congestive signs and symptoms, emerging as the preferred diuretic agents to use in most patients with advanced HF. As concerns patients with atrial fibrillation (n=342), 208 received an oral anticoagulant agent (181 warfarin and 27 a novel anticoagulant agent). Ninety patients with and 48 without atrial fibrillation took digoxin. Ivabradine was prescribed in 72 (7.3%) patients, 12 of them with a LVEF <35%.

Discussion and Conclusions

HF is an increasing health problem worldwide, with more than 21 million affected adults in the USA and Europe.[19] The reasons for this pandemic include the increasing amount of causative factors that lead to an alteration in left ventricular structure and function such as coronary artery disease and hypertension, the improvements in medical therapies resulting in prolonged life expectancy and first and foremost the ageing of the

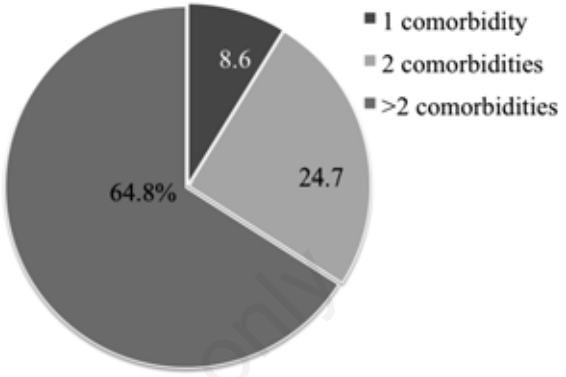

Figure 1. Distribution of the number of comorbidities registered at the time of hospital admission in those 975 patients with heart failure.

Table 1. General characteristics of the study population. In the brackets there are the percentages.

	Women (n=518)	Men (n=457)	P
Age (years; mean ± SD)	79.3±9.0	74.3±10.3	P<0.05
Gender	53.1%	46.8%	
Symptom severity			
NYHA I	16 (3.2)	15 (3.4)	ns
NYHA II	211 (42.4)	172 (40)	ns
NYHA III	226 (45.4)	195 (45.4)	ns
NYHA IV	44(8.8)	47 (10.9)	ns
ECG records			
Sinus rhythm	271 (52.3)	266 (58.2)	ns
Atrial fibrillation	202 (38.9)	147 (32.1)	P=0.02
Pacemaker rhythm	33 (6.4)	36 (7.9)	ns
Etiology			
Ischemic	265 (52.5)	282 (62.3)	ns
Non ischemic	239 (47.4)	170 (37.6)	P<0.002
LVEF			
<30%	13 (5.2)	38 (15.0)	P=0.0001
30%-50%	184 (73.9)	181 (71.2)	ns
>50%	52 (20.8)	35 (13.7)	P<0.05
Comorbidity			
COPD	213 (41.1)	269 (58.8)	P=0.0001
Diabetes	219 (42.3)	191 (41.7)	ns
Chronic kidney disease	193 (37.3)	155 (33.9)	P=0.005
Hypertension	422 (81.5)	328 (71.8)	P=0.0001
Liver disease	49 (9.4)	53 (11.5)	ns
CNS vascular disease	200 (38.6)	173 (37.8)	ns
Neoplasm	42 (8.1)	54 (11.8)	ns

SD, standard deviation; NYHA, New York Heart Association; ns, not statistically significant; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.

population, since HF prevalence follows an exponential pattern rising with age. Data from the *Kaiser Permanente System* comparing the incidence of HF in 1970-1974 and 1990-1994 among people aged ≥65 years indicated that the age-adjusted incidence increased by 14% over time and was greater for older people and for men.[20] In the Framingham Heart Study in the USA, it was estimated that in 1997 people aged over 65 years were 33 million (including approximately 7.9 million with age over 80 years-old) and that, by the year 2030, this number will rise to about 70 million (of which 18 million with age 80 years or older).[21] This trend was also confirmed by the comparison between data of CONFINE study[15] and of the previous TEMISTOCLE study,[22] carried out in Italian Internal Medicine Units, depicting that from 2002 to 2008 the mean age of patients admitted for HF went up from 77 to 79 years. These features are confirmed in another recent Italian study on 770 patients with HF observed in Internal Medicine wards, showing a mean age of 82.5 years.[23] Results of the present study agree with the above-mentioned data (mean age of 76.9 years, with 76% of patients older than 70 years). In a subgroup analysis in our whole series (Table 3), we observed several statistically significant age-differences as regards etiological factors, comorbidity and cardiac rhythm; all the same, some medications such as β-blockers, oral anticoagulant and double antiplatelet agents were significantly less frequent assumed in older patients. Various main factors may explain the high prevalence of HF in the elderly: progressive changes on an ongoing biological aging process, prolonged exposure to cardiovascular risk factors, comorbid conditions associated with ageing[24] and the availability of effective treatments in patients with acute coronary syndromes extends survival increasing the incidence of HF.[25]

Various comorbidities usually coexist in elderly patients and contribute to the development of HF, end stage heart disease and death ant this negative prognostic impact of concomitant diseases has been documented in several studies.[22-24,26] In the present survey we have observed that 64.9% patients had more than two chronic conditions, with a higher, but non-significant, prevalence in women. These results are quite similar to that of the above-mentioned Italian study.[23] The most frequent comorbidities we registered were arterial hypertension (76.9%), COPD 49.4% and diabetes (42%). Previous epidemiological studies demonstrated similar high prevalence of diabetes in patients with HF, that is nearly four time greater than the prevalence of diabetes in the general population.[27,28]

As concerns etiological factors, the most common worldwide-described causes of HF [coronary artery disease (CAD) and arterial hypertension][29-31] were confirmed in the present study. Surveys on chronic HF in the community have shown that 40% to 50% of patients present with a LVEF ≥50%.[32] In our study almost two/thirds of HF patients also presented with a

Table 2. Cardiovascular treatments registered at hospital admission in the whole series (975 patients).

	Total patients (% of 975)	Women	Men	P
β-blockers	510 (52.3)	272	238	0.05
Calcium-channel blockers	212 (21.7)	100	112	ns
ACE inhibitors	498 (51.0)	254	244	ns
Angiotensin receptor blockers	199 (20.0)	122	77	0.001
Loop diuretics	704 (72.2)	364	340	ns
Ivabradine	72 (7.4)	33	39	ns
Nitrates	242 (24.8)	130	112	ns
Digoxin	138 (14.2)	76	62	ns
Aldosterone antagonists	276 (28.3)	128	148	ns
Antiarrhythmics	93 (9.5)	48	45	ns
Ranolazine	23 (2.4)	14	9	ns
Warfarin	240 (24.6)	128	112	ns
DOA	34 (3.5)	17	19	ns
LMWH	75 (7.7)	41	34	ns
Antiplatelet agent	511 (52.4)	260	251	ns
Double antiplatelet agents	14 (1.5)	5	9	ns

ns, not statistically significant; ACE, angiotensin converting enzyme; DOA, direct oral anticoagulants; LMWE, low molecular weight heparin.

preserved EF (>40%). These patients were mostly elderly and women, with a history of hypertension, and other co-morbidities.

In the present study significant gender differences were registered with regards to comorbidity, LVEF values and drugs assumed at admission (Table 4).

Many recent studies focused attention on the controversial issue of the role of gender on HF prognosis. Gender differences are recognized in the incidence, clinical presentation, and mortality associated with cardiovascular disease.[33] Unfortunately, sex-specific diagnostic and treatment modalities have yet to gain similar attention which, in part, reflects incomplete understanding of physiological and cellular mechanisms contributing to gender differences in etiology of some cardiovascular diseases and failure to consider sex differences in pharmacokinetics and pharmacodynamics of drugs used to treat most cardiovascular diseases.[34,35] Progress in understanding these mechanisms is slow due to the continued use of male animals in many types of experiments, lack of reporting of the sex and hormonal status of animals and cells used in mechanistic studies, and the absence of reporting of clinical trial results by gender.[36-38]

Gender differences in HF have been reported in relationship with the underlying physiology related to the sexual differences in hormonal status, metabolism and so on.[39-41]

We also looked at the cardiovascular treatment and we can make some supposition about physician adherence to evidence-based therapy. Despite the ACE-Is represent the first-line drugs in HF, at admission only 51% of patients were on therapy with ACE-Is while 20.5% of patients were on angiotensin receptor blockers (ARBs). The underuse of these drugs can be explained by the high prevalence of old age and CKD, as reported also in CONFINE study.[15] In our study population, we did not observe statistically significant differences in

Table 3. Significant age-differences registered in the present study; data of whole series: 975 patients, 234 ≤70 years and 741 >70 years of age.

	≤70 years	>70 years	P
Etiology			
Ischemic	62.3	52.0	0.007
Non ischemic	37.6	47.9	0.007
Comorbidity			
Arterial hypertension	67.9	79.7	0.001
CNS vascular disease	24.7	42.6	0.001
ECG records			
Sinus rhythm	60.2	51.6	0.001
AF	25.6	41.4	0.001
LVEF <30%	21.6	5.9	0.001
Drugs at admission			
β-blockers	60.6	49.6	0.001
Nitrates	17.9	26.9	0.007
Double antiplatelet agents	4.2	0.9	0.001
OA in AF	75.0	54.0	0.001

Data are expressed in percentages. CNS, central nervous system; ECG, electrocardiogram; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; OA, oral anticoagulant.

Table 4. Significant gender differences registered in the present study; data of whole series: 975 patients, 518 women and 457 men.

	Women	Men	P
Comorbidity			
COPD	41.1	58.8	0.0001
Arterial hypertension	81.6	71.5	0.001
Chronic kidney diseases	37.3	33.9	0.005
LVEF <30%	5.2	15.0	0.001
Drugs at admission			
β-blockers in patients with LVEF <40%	64.0	75.8	0.003
Aldosterone antagonists in patients with LVEF	<35%	36.4 53.3	0.0001
Angiotensin receptor blockers	23.6	16.8	0.001

Data are expressed in percentages. COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

the prescription of ACE-I in patients < or >70 years, while in patients with age >70 years we have seen even greater prescription of ARBs (22.2% *vs* 14.9%; P=0.02). One can speculate that the wider use in older patients of ARBs than ACE-I may be related with the better general tolerability of the former class of drugs. Furthermore, we found no statistically significant differences in prescribing ACE-I and ARBs in patients with and without CKD. Several studies showed that worsening of renal function in the setting of ACE-I initiation appears to represent a benign event that is not associated with a loss of benefit from continued ACE-I therapy[42] and that prescription at the discharge of ACE-I or ARBs was associated with a significant modest reduction in all-cause mortality in older systolic heart failure patients with CKD including with more advanced CKD.[43] The most prescribed drugs were loop diuretics coherently with the presence of congestion in the majority of subjects. An aldosterone receptor antagonist was used in 28.30% of patients with EF <35% and still in NYHA class II or III despite treatment with an ACE-I or an ARB and a β-blocker.

β-blockers were prescribed in 52.3% of patients, without difference between patients with and without COPD. It is interesting to observe that in Italian CHF-register (2003-2005)[44] were reported a significant difference in β-blockers prescriptions between patients with and without COPD (34.4% *vs* 59.3% - P<0.0001); this occurrence may be in part related to the advent of selective β-blockers, too.[45] Only 18.5% of patients with AF were receiving warfarin and 2.7% were under prescription of a novel anticoagulant and this represents a low percentage considering the registered CHA_2DS_2-VASC score in our series. But, as it is well-known, the compound of different parameters considered in CHA_2DS_2-VASC score are also items of HAS-BLED score; so, patients with high thromboembolic risk are often also at increased risk of bleeding and therefore there is greater fear in the prescription of oral anticoagulants in these elderly and frail patients.

In contrast with the previous Italian study we also considered the use of Ivabradine whose clinical benefits have been demonstrated both in patients with stable CAD with associated systolic left ventricular dysfunction or in patients with congestive HF.[46]

In our series, 387 (39.6%) patients had almost one hospitalization in the previous twelve months. This occurrence witnesses the complexity and fragility of the patient included in the present study. This high rate of re-admissions is related to the poor therapeutic compliance and suboptimal adherence to current guidelines we found in our population.

In conclusion, our data show that advanced age and the presence of multiple comorbidities characterize, in the hospital *real life*, patients with HF admitted to Internal Medicine wards in our Region. In addition, these data highlight some significant differences related to age range and to gender and that drug prescriptions on the territory are only in partial agreement with the standards outlined by the current guidelines.

References

1. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123-33.
2. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317-27.
3. Loehr LR, Rosamond WD, Chang PP, et al. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 2008;101:1016-22.
4. MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. Circulation 2000;102:1126-31.
5. Mosterd A, Cost B, Hoes AW, et al. The prognosis of heart failure in the general population: the Rotterdam study. Eur Heart J 2001;22:1318-27.
6. Cowie MR, Wood DA, Coats AJ, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000;83:505-10.
7. Dharmarajan K, Hsieh AF, Lin Z, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013;309:355-63.
8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013 [Epub ahead of print].
9. Roger VL. Epidemiology of heart failure. Circ Res 2013;113:646-59.
10. Rengo F, Leosco D, Iacovoni A, et al. Epidemiology and risk factors for heart failure in the elderly. Ital Heart J 2004;5:9S-16S.
11. Douglas LM, Murali C. Harrison's principles of internal medicine. 18th ed. Chapter 234. Heart failure and cor pulmonale. St. Louis, Missouri: McGraw-Hill; 2013. pp 1882-1890.
12. Terzaet@. In Italia sempre più di anziani a rischio scompenso cardiaco; 2006. Available from: http://terzaeta.com/med/2006/gennaio/26.html
13. Ministero della Salute. Rapporto Annuale sull'attività di ricovero ospedaliero. Dati SDO 2012. Available from: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2094_allegato.pdf
14. Ministero della Salute. Rapporto Annuale sull'attività di ricovero ospedaliero. Dati SDO 2013. Available from: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2190_allegato.pdf
15. Biagi P, Gussoni G, Iori I, et al. CONFINE Study Group; Clinical profile and predictors of in-hospital outcome in patients with heart failure: the FADOI CONFINE Study. Int J Cardiol 2011;152:88-94.

16. Cavaliere R, Gallucci F, Mathieu G. La prevenzione cardiovascolare nello Scompenso Cardiaco, in: Position paper FADOI sulla prevenzione cardiovascolare nei pazienti complessi a rischio. Quaderni Ital J Med 2015;3:339-55.
17. Catapano A, Vanuzzo D. Epidemiologia nazionale e regionale. Commissione "Epidemiologia Nazionale e Regionale". G Ital Cardiol 2009;10:38S-57S.
18. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
19. Mozaffarian D, Benjamin EJ, Go AS, et al. for America Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. Circulation 2015;131:e29-e32.
20. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation 2006;113:799-805.
21. Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993;88:107-15.
22. Di Lenarda A, Scherillo M, Maggioni AP. Current presentation and management of heart failure in cardiology and internal medicine hospital units: a tale of two words - the TEMISTOCLE study. Am Heart J 2003;146:E12.
23. Verdiani V, Panigada G, Fortini A, et al. for the SMIT Study Group. The hearth failure in internal medicine in Tuscany: the SMIT study. Ital J Med 2015;9:349-55.
24. Bodh IJ. Aging and heart failure: mechanisms and management. Chapter I: Changing demographics of the aging population with heart failure and implications for therapy. Berlin: Springer; 2014. pp 1-14.
25. Formiga F, Ferrer A, Mascarò J, et al. Predictive items of one year mortality in nonagenarians. The Nonasanfeliu study. Aging Clin Exp Res 2007;19:265-8.
26. Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. Am J Med 2011;124:136-43.
27. MacDonald MR, Petrie MC, Hawkins NM, et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J 2008;29:1224-40.
28. Kapoor JR, Fonarow GC, Zhao X, et al. Diabetes, quality of care, and in-hospital outcomes in patients hospitalized with heart failure. Am Heart J 2011;162:480-6.e3.
29. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117:2544-65.
30. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.
31. Fabbri G, Gorini M, Maggioni AP, et al. Italian network on congestive heart failure: ten-year experience. G Ital Cardiol 2006;7:689-94.
32. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2005;47:320-32.
33. Greiten LE, Holditch SJ, Arunachalam SP, Miller VM. Should there be sex-specific criteria for the diagnosis and treatment of heart failure? J Cardiovasc Trans Res 2014;7:139-55.
34. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 Update: a guideline from the American Heart Association. Circulation 2011;123:1243-62.
35. Seeland U, Regitz-Zagrosek V. Sex and gender differences in cardiovascular drug therapy. Handb Exper Pharmacol 2012;214:211-36.
36. Zucker I, Beery AK. Males still dominate animal studies. Nature 2010;465:690.
37. Taylor KE, Vallejo-Giraldo C, Schaible NS, et al. Reporting of sex as a variable in cardiovascular studies using cultured cells. Biol Sex Differ 2011;2:11-5.
38. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes 2010;3:135-42.
39. Misuraca G, Di Tano G, Camerini A, et al. Ricercatori IN-HF Outcome. Data from the IN-HF Outcome registry. G Ital Cardiol 2012 May;13:23S-30S.
40. Gronda E, Aronica A, Visconti M, et al. Gender differences of at risk patients with overt heart failure in the real world of general practice. Data from the GIPSI (Gestione Integrata Progetto Scompenso in Italia) registry. G Ital Cardiol 2010;11:233-8.
41. Lam CS, Carson PE, Anand IS, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circulation Heart Fail 2012;5:571-8.
42. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function following initiation of angiotensin converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail 2011;4:685-91.
43. Ahmed A, Fonarow GC, Zhang Y, et al. Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease. Am J Med 2012;125:399-410.
44. Fabbri G, Gorini M, Maggioni AP. IN-CHF: il registro italiano dello scompenso cardiaco. Dieci anni di esperienza. G Ital Cardiol 2006;7:689-94.
45. Fabbri G, Gorini M, Maggioni AP, et al. Heart failure: critical patients. G Ital Cardiol 2007;8:568-73.
46. Lupi A, Rognoni A, Cavallino C, et al. Ivabradine for treatment of coronary artery disease: from last chance resort to mainstem of a reasoned therapy. Cardiovasc Hematol Agents Med Chem 2014 [Epub ahead of print].