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GENDER DIFFERENCES IN AN ITALIAN REAL-WORLD COHORT WITH HEART FAILURE: FINDINGS FROM 41 413 PATIENTS OF THE ARNO DATABASE

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ABSTRACT

BACKGROUND. The real-world evidence of Italian outpatients with heart failure (HF) has been explored using the ARNO database, including more than 40,000 patients.

METHODS. This retrospective analysis of the ARNO HF patients explored gender differences in the clinical and therapeutic characteristics, one-year outcomes and health expenditure.

RESULTS. Women were 51.4% of the sample, on average older than men and had developed the disease later in life. Males had significantly higher rates of prior hospital admissions for acute coronary syndrome and higher prescriptions of CV medications. Women suffered more frequently from depression but less from diabetes and COPD. Women showed significantly better 1-year outcome in terms of re-hospitalizations, both for CV and non-CV causes, but not lower mortality. Health costs were lower for women, being hospitalizations the major driver of costs in HF.

CONCLUSION. This analysis revealed gender differences in HF patients, suggesting the need for more gender-specific studies to develop gender-driven management approaches.

KEYWORDS : Heart failure, gender differences, real-world database

INTRODUCTION

Heart failure (HF) is a major cause of morbidity and mortality and is recognized as a major public health problem worldwide, affecting approximately 2% of the population in developed countries, up to 10% among people >70 years of age(Bui, Horwich & Fonarow, 2011; Benjamin et al., 2019, Ponikowski et al., 2016; Maggioni et al., 2016). Approximately half of HF patients are women and substantial gender differences have been reported in HF epidemiology, pathophysiology, and outcome(Stein et al., 2013; Dunlay et al., 2013; Nakada et al., 2016). Such differences have been underlined by the European Society of Cardiology Guidelines since 2012, together with the increasing prevalence of some predisposing factors for HF among women, such as atrial fibrillation (AF), anemia and obesity (Ponikowski et al., 2016). However, despite these recognized sex differences, women are generally under-represented in clinical trials, and community-based studies of HF patients suggested underutilization of evidence-based therapies in females (Benjamin et al., 2016; Meta-analysis Global Group in Chronic Heart Failure, 2012; Stramba-Bodiale, 2010). It has been reported that women with chronic HF (CHF) have better survival than men (Ghali et al., 2003; O'Meara et al., 2007; Lam et al., 2012; Deswal & Bozkurt, 2006). However, within 6 years of HF diagnosis, 46% of adult women have been reported with significant disability, compared with only 22% of men (Philbin & DiSalvo, 1998). Gender has been shown to be an important determinant of the length of hospital stay, hospital charges, and intra-hospital mortality (Philbin & DiSalvo, 1998). Women who have been hospitalized with HF have less improvement in physical health status and perceive their quality of care to be lower than that of males (Chin & Goldman, 1998). Overall, it seems that HF has different characteristics in men and women, and it may be hypothesized that clarifying sex-specific differences in HF might drive different therapeutic and preventive approaches to the disease (Jessup & Piña, 2004).

In Italy, the real-world evidence of HF has been explored using the ARNO administrative database that includes the population of five Local Health Units of the INHS (Maggioni et al., 2003). The analysis involved all patients discharged for HF with at least one prescription for HF with the aim to describe the characteristics of HF patients occurring in the hospital clinical practice compared to those of patients randomized in controlled trials, who are generally highly selected and not enough representative of the 'real world'. We here report the results of a gender analysis of the same database, performed in order to explore possible gender-differences in the demographic, clinical and therapeutic characteristics of the Italian real-life HF population, as well as one-year outcomes and overall health expenditure.

MATERIAL AND METHODS

The ARNO Observatory (http://osservatorioarno.cineca.org) is a population-based database that, since 1987, collects administrative data of five Local Units of the INHS, with a population of 2,456,739 inhabitants. Included data are patient demographics, outpatient drug prescriptions, hospital discharge diagnoses, imaging, laboratory tests, and prescriptions. Prescription data were derived from the INHS reimbursed drug prescriptions database; therefore, medicines prescribed and purchased privately were inevitably lost.

A previous report had considered, from the overall 5-LHU population, 54,059 patients hospitalized for HF (representing 2.2% of the overall population) during the accrual period, from January 1st, 2008 to December 31st, 2012 (Maggioni et al., 2003). These patients had been selected based on at least one ICD-9 (International Classification of Diseases-Ninth Revision) code identifying hospital discharges with primary or secondary HF diagnosis. Of these patients, 41,413 were discharged alive and prescribed at least one treatment for HF and represented our study population (Maggioni et al., 2003). Study patients were followed up to 1 year after the index hospital discharge with primary or secondary diagnosis of HF (index event/index date).

PATIENTS' CHARACTERISTICS ANALYZED BY GENDER

As demographic data, age and sex distribution were analyzed. The patients' clinical characteristics, hospitalizations due to cardiovascular reasons (including HF, acute coronary syndrome [ACS], and stroke/transient ischemic attack [TIA]), as well as the presence of all comorbidities (renal failure, diabetes, depression, tumors, or COPD) during one year before the index date were calculated by gender. Number and duration (total number of days spent in hospital during the 12 months after index discharge) of rehospitalizations, categorized as due to CV and non-CV causes, and in-hospital all-cause mortality during first hospitalization and follow-up rehospitalizations were also evaluated by gender.

Concerning medications, measured indicators were the prescriptions of ACEIs/ ARBs, beta-blockers, potassium (K)-sparing agents, and cardiac glycosides as HF-specific drugs during follow-up. Non-HF specific medications were also analyzed by sex.

The following healthcare costs were calculated during the 1-year follow-up period: drugs reimbursed by the INHS (calculated at the public prices reimbursed by the INHS), diagnostic and therapeutic procedures (considering Italian national fares), and days of hospitalization (considering Italian national fares for the supply of hospital care, DRGs-TUC 2008).

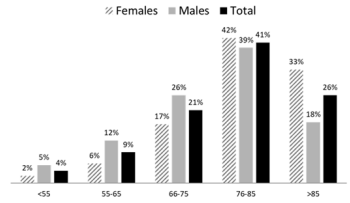
The male and female patient populations were compared by the Student's t-test for quantitative variables, and Chi-square test for qualitative variables. The accepted level of significance was set to 0.05. The Bonferroni's correction was considered when commenting results

RESULTS

Patient characteristics

Of the 41,413 patients hospitalized for HF during the recruitment period, 49% were men and 51% women. Mean age was 77.99 (SD 10.98) years for the overall population, 80.37 (10.08) for women, and 75.46 (11.42) for men ($p < 0.001$). As shown in Figure 1, the ratio of women vs men increases with age, with women becoming predominant after the age of 75 ($p < 0.00001$).

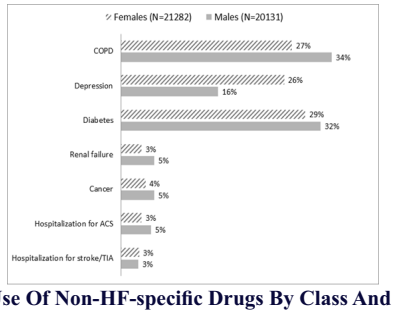
Fig. 1. Sex distribution of HF patients among age groups.



	<55	55-65	66-75	76-85	>85	Total
Females	446	1,220	3,639	8,965	7,012	21,282
Males	1,043	2,483	5,137	7,906	3,562	20,131
Total	1,489	3,703	8,776	16,871	10,574	41,413

The most common comorbidities recorded the year before the index HF hospitalization were diabetes (31%), COPD (30.5%), and depression (21%). Comparing comorbidities by gender, diabetes and especially COPD were more common among men (32% vs 29%, and 34% vs 27%, respectively; $p < 0.00001$ in both cases), whereas depression was much more frequent among women (26% vs 16%, $p < 0.00001$; figure 2).

Fig. 2. Clinical conditions recorded in HF patients during 1 year before the index hospitalization for HF.



ACS: acute coronary syndrome; COPD: Chronic obstructive pulmonary disease; HF: heart failure; TIA: transient ischemic attack.

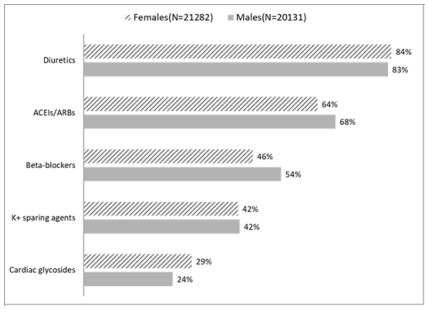
Prior hospital admissions for an ACS were more frequent among men (4.82%) than in women (3.23%; $p < 0.00001$), whereas hospitalizations for stroke/TIA were rather balanced between sexes ($p = 0.54$).

Almost half of patients (49.7%) had been discharged with a HF diagnosis (index event) from a general medicine department (55% of women and 45% of men; $p < 0.00001$), 20% from a cardiology department (16%, of women and 23.5% of men; $p < 0.00001$), and 14% from a geriatric department (15% of women and 12% of men; $p < 0.00001$). More men (9.4%) than women (4.3%) were discharged from a Coronary Care Unit ($p < 0.00001$).

FOLLOW-UP DATA

The most prescribed medications in the overall population in the 12 months following index discharge were diuretics (in 83% of patients), followed by ACEIs/ARBs (66%), beta-blockers (50%), K-sparing agents (42%), and cardiac glycosides (27%). Some differences emerged analyzing HF-specific drug prescriptions by sex (figure 3): ACEIs/ARBs and beta-blockers were prescribed more commonly in men, while digitalis use was more common among women (chi-square p-value < 0.00001 for each comparison).

Fig. 3. Use of HF-specific drugs in HF patients by class and sex.



ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers; HF: heart failure.

Among non-HF-specific therapies, the most commonly prescribed medications were proton-pump inhibitors (PPIs), slightly more common in women (83%) than in men (80%), followed by antiplatelet agents, more prescribed in men (65%) than in women (59%) (table 1).

Table 1 – Use Of Non-HF-specific Drugs By Class And Sex During 12 Months After Index Discharge

Medication class	Women (N=21,282)		Men (N=20,131)		Chi-square p-value
	N	%	N	%	
PPIs	17,695	83.1	16,105	80	<.00001
Antiplatelets	12,543	58.9	13,120	65.2	< .00001
Quinolones	8,424	39.6	8,507	42.3	< .00001
Statins	6,609	31.1	8,895	44.2	< .00001
Antigout	6,947	32.6	7,583	37.7	< .00001
LMWHs	7,189	33.8	6,127	30.4	< .00001
Nitrates	6,752	31.7	6,448	32	0.5072
Penicillins	6,517	30.6	6,473	32.2	0.0008
NSAIDs	7,019	33	5,754	28.6	<.00001
Systemic corticosteroids	6,494	30.5	5,787	28.7	0.0001
Vitamin K antagonists	5,703	26.8	5,920	29.4	< .00001
Cephalosporins	5,160	24.2	4,736	23.5	0.0860
Vascular Ca+-channel-blockers	4,494	21.1	4,373	21.7	0.1328
Opioids	5,087	23.9	3,455	17.2	<.00001
Oral hypoglycemic agents	4,168	19.6	4,210	20.9	0.0008
Aerosol combined adrenergic agonists	3,475	16.3	4,167	20.7	<.00001
Aerosol corticosteroids	3,802	17.9	3,755	18.7	0.0380
SSRI antidepressants	4,249	20	2,624	13	<.00001
Anti-arrhythmics	2,973	14	3,640	18.1	<.00001
Aerosol anti-cholinergic bronchodilators	2,712	12.7	3,715	18.5	<.00001

During the 1-year follow-up, 36% of the patients were readmitted to hospital for CV causes and 34% for non-CV causes, with 1.7 re-admissions per hospitalized patients. Rehospitalizations were significantly more frequent among men than among women, especially for CV causes (40% vs 33%), but also for non-CV causes, even though difference was smaller (35% vs 33%; table 2).

Table 2 – Rehospitalizations of HF patients during the 1-year follow-up by discharge diagnosis and sex

Discharge diagnosis		Women			Men			Chi-Square p-value
		N (%) of discharged patients	Nr of discharges per hospitalized pt.	Mean hospital stay (days)	N (%) of discharged patients	Nr of discharges per hospitalized pt.	Mean hospital stay (days)	
CV causes	CHF	3,972 (18.7)	1.39	17	3,975 (20.0)	1.34	15	0.0052
	Other vascular diseases	2,969 (13.9)	1.34	18	4,121 (19.3)	1.48	17	<.00001
	ACS	700 (3.3)	1.23	13	1,014 (4.9)	1.26	13	<.00001
	Stroke/TIA	805 (3.8)	1.14	15	686 (3.3)	1.17	14	0.0407
Total CV causes		**6,962 (32.7)**	**1.62**	**20**	**7,947 (39.5)**	**1.69**	**19**	**<.00001**
Non-CV causes	Respiratory diseases	2,496 (12.8)	1.38	19	2,826 (14.0)	1.46	19	<.00001
	Traumas and poisonings	1,210 (5.1)	1.31	23	890 (4.4)	1.27	18	<.00001
	Digestive diseases	938 (4.6)	1.21	14	971 (4.8)	1.23	12	0.0437
	Genito-urinary diseases	757 (4.2)	1.18	14	978 (4.9)	1.29	13	<.00001
	Tumors	675 (4.1)	1.26	17	1,031 (5.1)	1.3	17	<.00001
	Ostheo-muscle-connective tissues diseases	617 (2.6)	1.14	29	468 (2.3)	1.17	27	0.0003
	Badly defined conditions	490 (2.6)	1.09	15	574 (2.9)	1.1	11	0.0004
	Infectious diseases	497 (2.3)	1.12	15	439 (2.2)	1.15	15	0.2901
	Endocrine and metabolic diseases	518 (2.1)	1.08	12	339 (1.7)	1.1	13	<.00001
	SNC and sense organs diseases	303 (1.4)	1.18	19	293 (1.5)	1.16	18	0.7864
	Others	243 (1.2)	1.04	23	271 (1.4)	1.27	18	0.0604
	Hematologic diseases	229 (1.1)	1.05	12	214 (1.1)	1.11	13	0.8978
	Psychiatric diseases	161 (0.7)	1.25	22	129 (0.6)	1.38	23	0.1582
	Skin and subcutaneous tissue diseases	128 (0.6)	1.15	17	100 (0.5)	1.17	19	0.1501
	Congenital malformations	21 (0.1)	1.63	14	29 (0.1)	1.45	17	0.1838
Total non-CV causes		**7,047 (33.1)**	**1.63**	**24**	**7,091 (35.2)**	**1.74**	**23**	**<.00001**
Total		**11,353 (53.3)**	**2.01**	**27**	**12,078 (60)**	**2.14**	**26**	**<.00001**

Chi-square's p-value is referred to the proportion of discharged patients in men vs women for each cause

No remarkable difference was observed for mean overall duration of hospital stay between men and women: 19 vs 20 days respectively for CV causes and 23 vs 24 days respectively for non-CV causes. In terms of hospital departments, men were more frequently admitted to cardiology departments than women (19% vs 10%).

Overall costs were somewhat higher for men than for women (table 3): mean annual expense per population unit was 13,273 € vs 10,451 € (table 3).

Table 3 – Overall costs of HF patients by sex

Expense items	Women (N=21282)				Men (N=20131)			
	Annual mean expense per population unit (€)	%	Annual mean expense per population unit (€)		Annual mean expense per population unit (€)	%	Annual mean expense per population unit (€)	
			1st discharge	Follow- up			1st discharge	Follow- up
Medications								
non-HF-specific	946.00	9.1	16.00	930.00	1,157.00	8.7	19.00	1,138.00
HF-specific	132.00	1.3	3.00	129.00	147.00	1.1	3.00	144.00
Hospitalizations	8,859.00	84.8	3,944.00	4,915.00	11,223.00	84.6	4,891.00	6,332.00
Diagnostic/specialistic exams	514.00	4.9	1.00	513.00	746.00	5.6	2.00	744.00
Total	**10,451.00**	**100.0**	**3,964.00**	**6,487.00**	**13,273.00**	**100.0**	**4,915.00**	**8,358.00**

Note: First Discharge is the index event

Overall in-hospital mortality during the index hospitalization was slightly higher for women (10.1%) than for men (9.5%), whereas it was similar during follow-up re hospitalizations (10.7 vs 10.4%; table 4).

Table 4 – Overall 1-year intrahospital mortality in HF patients by sex

Intrahospital mortality	Total N = 54,059		Women N = 28,202		Men N = 25,857		Chi-square p-value
	N	%	N	%	N	%	
At 1st hospitalization (index event)	5,298	9.8	2,844	10.1	2,454	9.5	0.0203
Rehospitalizations during follow-up	4,533	10.9	2,250	10.6	2,283	11.3	0.0004
Lost to follow-up after 1st and 2nd quarter*	4,373	10.6	2,280	10.7	2,093	10.4	0.9661

* include deceased patients and those transferred to other hospitals or in long-term care centers (3.2% of females and 2.5% of males)

Chi-square's p-value is referred to the comparison of each mortality event in men vs women

DISCUSSION

In the present analysis from an Italian administrative database we report the gender differences observed in a real-world cohort of over 40,000 patients hospitalized for HF from 2008 to 2012. Women represented slightly more than a half of the patient population, consistently with some papers, but not with others reporting lower rates for women, ranging from 30 to 45% (Jessup & Piña, 2004; Taylor, 2015; Ibrahim, Burant & Kent Kwoh,2003; Parissim et al.,2013; Stein et al., 2013). Women with HF in our cohort were on average older than men, and actually developed the disease later, with 75% of them being aged >75 years compared to 57% of men, and 33% being older than 85 compared to 18% of men. Despite being on average 5 years older, women seem to have a slightly better unadjusted 1-year outcome then men in terms of rehospitalizations, both for CV and non-CV causes, though crude mortality was quite similar in both sexes. Literature data on mortality are very controversial: very similar mortality data with no relevant differences between sexes had been reported in previous surveys, whereas older data claimed a worse prognosis in women both in terms of mortality and hospital admissions, and other authors support a better survival in women than in men (Ibrahim et al.,2003; Parissim et al.,2013; Stein et al., 2013; Benjamin et al., 2019; Philbin & Bozkurt, 2006; Jessup & Piña, 2004; Ghali et al., 2003; O'Meara et al., 2007; Lam et al., 2012; Deswal & Bozkurt, 2006) .

Interesting between genders differences in comorbid conditions emerged in our cohort. Depression is a strikingly common comorbidity in CHF patients. Twenty-one percent of patients in our overall cohort had a diagnosis of depression in the year before the index admission , putting depression in the third place as concomitant condition after diabetes and COPD, and a high prevalence of this condition has been widely reported also in the literature, with depressive symptoms reported in up to 65% of HF patients in a recent paper (Ghanasekaran, 2011; Newhouse & Jiang, 2014; Wallenborn & Angermann, 2014; Kao et al., 2014). It is not surprising that depression was more prevalent among women in our study population, being depression and other affective disorders generally more common in women, even though the difference tends to decrease with age (Faravelli, Scarpato, Castellini & LoSauro, 2013; Forlani et al., 2014; Parker & Brotchie, 2010). On the contrary, diabetes and especially COPD were more common among male HF patients. COPD is generally recognized as a "disease of men". However, prevalence tends to balance in both sexes in recent years, possibly due to increasing tobacco consumption among women, but maybe also because of a differential susceptibility to tobacco, anatomic, hormonal, and behavioral differences, and differences in response to available therapeutic modalities (Aryal, Diaz-Guzman & Mannino, 2013; Roberts, Partel & Partridge, 2016). Concerning diabetes, men are well known to have a higher risk than women for type 2 diabetes, and the historical male predominance has even increased over time reaching a male/female ratio up to 2 in some cohorts (Wändell & Carlsson, 2014; Sattar, 2013). The gap was not so marked in our HF cohort, but the difference between sexes has been reported to be higher especially in the age 45-64 years, whereas our patients were older. Furthermore, it is worth underlining that our male population had had more frequently coronary heart disease events, as shown by 50% more men admitted to hospital for an ACS both during the 12 months preceding the HF index hospitalization and the 12-month follow-up, and more men were admitted to cardiology departments both at first and at follow-up hospitalizations. On the other hand, cerebrovascular diseases, namely strokes and TIAs, were 15% more common in women.

The higher prevalence of prior CV events in men was also mirrored by medication prescriptions, which were higher in men for antithrombotic agents. Regarding statins, interestingly a recent retrospective analysis investigating gender differences in statin therapy found that, in patients with HF, female gender is independently associated with lower statin prescription rates, although statin therapy in HF patients has been shown to be associated with improved survival in both genders (Ballo et al., 2016). It is also unclear why more women are prescribed cardiac glycosides, especially considering that a retrospective analysis of the Digitalis Investigation Group (DIG) study showed that digoxin was associated with a higher risk of mortality in women, especially at higher doses (Adams et al., 2005; Juillière, Berder, Brembilla-Perrot & Selton-Suty, 2004). On the other hand, it is consistent with the registered comorbidities that bronchodilators were more prescribed in men and antidepressants in women. Interestingly, PPIs were the most commonly prescribed non-HF-specific drugs in both sexes. Actually, PPIs are among the most widely used non-cardiac medication classes in HF patients (Charlot et al., 2010; Ray et al., 2010; Rassen, Choudhry, Avorn & Schneeweiss, 2009; Schillinger et al., 2007; Oudit, Bakal, McAlister & Ezekowitz, 2011).

Last but not least, differences between genders emerged also in terms of costs. As reported in the original paper by Maggioni et al., the major driver of costs in HF is hospitalization (Maggioni et al., 2013). Thus, the higher costs of HF in men are clearly explained by the higher number of hospital admissions in general, and in Coronary Care Units in particular.

Our study has the limitations inherent to most administrative databases. This approach limited the number and type of variables available for the analysis. The most relevant missing variables are hypertension and atrial fibrillation, usually more prevalent among older women among the causes of HF, which might, at least in part, account for the more favorable outcome of women, as compared to ischemic heart disease, which is more prevalent among men, as also shown by our data. Therapeutic compliance has also not been measured by gender in the ARNO database, which may hamper interpretation of the data with regard to this specific issue. On the other hand, this type of database has the advantage of providing information about a real-life population – shown to be very different from the cohorts usually recruited in interventional randomized clinical trials (RCTs) – and reliable long-term data about medication use and hospitalizations(Maggioni et al., 2013).

IMPLICATION FOR PRACTICE AND/OR POLICY

This post-hoc gender analysis of a real-world study in patients with heart failure points out important differences between sexes in terms of comorbidities, pharmacological treatment and risk of hospitalization that should be taken into consideration for a patient-tailored management of heart failure.

CONCLUSIONS

In conclusion, our gender analysis of the ARNO administrative database regarding Italian real-world HF patients revealed that women tend to develop HF later in life compared to men, suffer more frequently from depression, but less frequently from diabetes and COPD, have less re-hospitalizations thus implying lower costs for the INHS, and show no differences in 1-year mortality. This latter conclusion does not take into account a 5-year difference in age between men and women. In terms of pharmacological therapies, some differences emerged between sexes that are worth further investigation in a specifically designed analysis, because the main scope of gender analyses should be driving better patient-tailored treatments. There is increasing evidence in the literature that there are important sex differences in HF. However, most RCTs continue to enroll a large majority of men in their patient population (Pfeffer et al., 2003; McMurray et al., 2014; Teerlink et al., 2013). We believe that more gender-specific studies are needed in HF and other CV diseases in order to develop more appropriate gender-driven therapeutic approaches.

AUTHOR DISCLOSURE STATEMENT

The authors meet the criteria of the International Committee of Medical Journal Editors (ICMJE) for authorship and were fully responsible for all aspects of manuscript development.

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