Gender differences in the development of heart failure after acute coronary syndrome: Insight from the CORALYS registry

Edoardo Elia [a,b], Francesco Bruno [a,*], Gabriele Crimi [b], Wojciech Wańha [c], Sergio Leonardi [d], Mattia Mauro [a], Sergio Raposeiras Roubin [e], Enrico Fabris [f], Giuseppe Giannino [a], Massimo Mancone [g], Paolo Severino [g], Alessandra Truffa [h], Ovidio De Filippo [a], Zenon Huczek [i], Maciej Mazurek [i], Nicola Gaibazzi [j], Alfonso Ielasi [k], Bernardo Cortese [l,t], Andrea Borin [a], Iván J. Núñez-Gil [m], Giorgio Marengo [a], Daniele Melis [a], Fabrizio Ugo [n], Matteo Bianco [o], Lucia Barbieri [p,u], Federico Marchini [q], Piotr Desperak [c], Nuccia Morici [r], Marco Scaglione [h], Mariusz Gąsior [c], Guglielmo Gallone [a], Clara Lopiano [s], Giulio Stefanini [s], Gianluca Campo [q], Wojciech Wojakowski [c], Emad Abu-Assi [e], Gianfranco Sinagra [f], Gaetano Maria de Ferrari [a], Italo Porto [b], Fabrizio D'Ascenzo [a]

[a] *Division of Cardiology, "Città della Salute e della Scienza di Torino" Hospital, Department of Medical Sciences, University of Turin, Turin 10126, Italy*
[b] *DICATOV-Cardiothoracic and Vascular Department, San Martino Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy*
[c] *3rd Department of Cardiology, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland.*
[d] *Coronary Care Unit, Fondazione IRCCS Policlinico San Matteo, Italy*
[e] *Hospital Universitario Álvaro Cunqueiro, Vigo, Spain*
[f] *Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Trieste, Italy*
[g] *Dipartimento di Scienze Cliniche Internistiche, Anestesiologiche e Cardiovascolari, Sapienza Università di Roma, Rome, Italy,*
[h] *Division of Cardiology, Ospedale Cardinal G. Massaia, Asti, Italy*
[i] *1st Department of Cardiology, Medical University of Warsaw, Warszawa, Poland*
[j] *Cardiology Department, Parma University Hospital, Parma, Italy*
[k] *U.O. di Cardiologia Clinica ed Interventistica, Istituto Clinico Sant'Ambrogio, Milan, Italy*
[l] *Cardiovascular Research Team, San Carlo Clinic, Milano, Italy*
[m] *Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain*
[n] *Department of Cardiology, Sant'Andrea Hospital, Vercelli, Italy*
[o] *Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Turin, Italy.*
[p] *Division of Cardiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[q] *Cardiovascular Institute, Azienda Ospedaliero Universitaria di Ferrara, Cona (FE), Italy*
[r] *IRCCS S. Maria Nascente-Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy*
[s] *IRCCS Humanitas Research Hospital, Rozzano-Milan, Italy*
[t] *Fondazione Ricerca e Innovazione Cardiovascolare, Milano, Italy*
[u] *University of Milan, Milan, Italy*

A B S T R A C T

Background: Impact of gender on heart remodeling after acute coronary syndrome (ACS) and consequently on development of heart failure (HF) remains to be elucidated.
Methods: CORALYS is a multicenter, retrospective, observational registry enrolling consecutive patients admitted for ACS and treated with percutaneous coronary intervention. HF hospitalization was the primary endpoint while all-cause mortality and the composite endpoint of incidence of first HF hospitalization and cardiovascular mortality were the secondary ones.
Results: Among 14,699 patients enrolled in CORALYS registry, 4578 (31%) were women and 10,121 (69%) males. Women were older, had more frequently hypertension and diabetes and less frequently smoking habit. History of myocardial infarction (MI), STEMI at admission and multivessel disease were less common in women. After median follow up of 2.9 ± 1.8 years, women had higher incidence of primary and secondary endpoints and

* Corresponding author.
E-mail address: cescobruno@hotmail.it (F. Bruno).

female sex was an independent predictor of HF hospitalization (HR 1.26;1.05–1.50; $p = 0.011$) and cardiovascular death/HF hospitalization (HR 1.18;1.02–1.37; $p = 0.022$). At multivariable analysis women and men share as predictors of HF diabetes, history of cancer, chronic kidney disease, atrial fibrillation, complete revascularization and left ventricular ejection fraction. Chronic obstructive pulmonary disease (HR 2.34;1.70–3.22, $p < 0.001$) and diuretics treatment (HR 1.61;1.27–2.04, $p < 0.001$) were predictor of HF in men, while history of previous MI (HR 1.46;1.08–1.97, $p = 0.015$) and treatment with inhibitors of renin-angiotensin system (HR 0.69;0,49–0.96 all 95% CI, $p = 0.030$) in women.

Conclusions: Women are at increased risk of HF after ACS and gender seems to be an outcome-modifier of the relationship between a variable and primary outcome.

1. Introduction

Coronary artery disease (CAD) is a well-known contributor to heart failure (HF) incidence, as ischemic cardiomyopathy (ICM) is still the most frequent cause of HF with reduced ejection fraction (HErEF) [1,2]. However, it remains unclear if gender-related differences could play a role in HF development after acute coronary syndrome (ACS). Among genders, different burden and distribution of coronary atherosclerosis have been historically reported: male patients showed a heavy prevalence of atherothrombotic disease, whereas in women non-obstructive CAD, small and diffuse disease, coronary artery dissection and microvascular dysfunction are more common [3,4]. Finally, CAD in women is usually underdiagnosed and undertreated due to atypical clinical presentation, as commonly referred to as Yentl syndrome [5].

However, the impact of these CAD pathophysiological differences between men and women into HF development is partially unknown. Moreover, women are poor represented in current HF trials and studies, representing a gap in literature which is difficult to fill. Consequently, we performed a retrospective multicenter analysis of patients from the CORALYS registry to evaluate the role of gender difference on first HF hospitalization, overall and cardiovascular (CV) mortality after an ACS.

2. Methods

The CORALYS registry (NCT 04895176) is a retrospective, multicenter and observational study including consecutive patients admitted for ACS in 16 European Centers from 2015 to 2020. Patients were considered eligible if all the following criteria were met: 1) age > 18 years old, 2) ACS diagnosis (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI] and unstable angina [UA]), 3) ACS treatment with PCI. All patients who had prior to the index ACS hospitalization history of congestive heart failure, previous HF hospitalizations or reduced left ventricular ejection fraction (LVEF) < 50% were excluded. Where required, study investigators received approval from their local institutional boards or ethic committees.

2.1. Definitions

Demographics, clinical and angiographic data were retrospectively collected from previous medical records and abstracted on pre-specified electronic forms. The following variable were collected: CV risk factors, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), malignancies, peripheral artery disease (PAD) and the history of previous myocardial infarction (MI) or myocardial revascularization and stroke. An estimated glomerular filtration rate < 60 ml/min/1.73 m2 according to the Modification of Diet in Renal Disease (MDRD) equation was defined as chronic kidney disease (CKD). Definitions of STEMI, NSTEMI, UA and cardiogenic shock were made according to European Society of Cardiology (ESC) guidelines [6,7]. Major bleedings were defined as Bleeding Academic research Consortium 3,5 bleedings [8]. Multivessel disease (MVD) was defined as more than one coronary vessel with critical stenosis (≥70% diameter stenosis at angiographic evaluation or vessels with flow-limiting lesions as assessed by intracoronary physiology, both resting or hyperemic indexes). The definition of complete revascularization was no residual critical stenosis after PCI. Through transthoracic echocardiography with bidimensional Simpson formula were assessed left ventricular ejection fraction (LVEF). PCI was performed according to ESC guidelines and standard local practice. Dual antiplatelet therapy was prescribed to all patients that also received other treatment, including beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) and mineralocorticoid receptor antagonist (MRA), at discretion of the treating clinicians.

Follow-up data were collected from electronic medical records, visits at outpatient clinics, telephonic contact or formal query to the primary care physicians.

2.2. End points

The primary endpoint was the incidence of a first hospitalization for HF after the index ACS. All-cause death and the composite of first hospitalization for HF or cardiovascular (CV) death were the secondary endpoints. Further, clinical and procedural predictors of the primary and secondary end-points were assessed.

2.3. Statistical analysis

Continuous and categorical variables are reported as mean and standard deviation or median and interquartile range (IQR) and as frequencies and percentages, respectively.

Differences in clinical and procedural features between patients who experienced an HF admission at FU and those who did not were assessed with One-way Analysis of Variance (ANOVA) and chi-square test for continuous and categorical variables, respectively.

The actuarial survival curves and the related cumulative incidence curves were obtained with the Kaplan-Meier method for primary endpoint, all-cause death, CV death or HF hospitalizations stratified according to sex. A propensity score (PS) was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with sex as dependent outcome. Pairs of patients were derived using greedy 1:1 matching with a caliper of width of 0.2 standard deviation of the logit of the PS. A Cox regression model, stratified by the propensity was used for survival analysis. To assess whether the distributions of baseline covariates are similar between treatment arms after the application of the PS methods, the distribution of propensity scores for each treatment group was visually examined, demonstrating good overlap between groups, Supplemental Fig. 1. In addition, the *pstest* command in STATA was used for testing balance in the PSM population.

Predictors of primary and secondary endpoints were identified using a proportional risk model of Cox, with a calculation of their respective hazard ratio (HR) and their confidence interval (CI) at 95%. A multivariable Cox regression model was built to identify the parameters independently associated with the occurrence of primary and secondary endpoints at follow-up; covariates with lower than 50% of missing data, with a statistically significant association with endpoints at the univariable analysis with a $p < 0.10$ and clinically relevant covariates were

included in the final model [9]. Only two tail p-value <0.05 were considered statistically significant. Analyses were performed with SPSS® Statistics v24 and STATA v17 (StataCorp, College Station, Texas).

3. Results

3.1. Baseline characteristics

A total of 14,699 patients were included in the final population: 4578 (31.1%) women and 10,121 (68.9%) males and the mean follow-up was 3.9 years. Baseline clinical characteristics of the entire cohort and according to gender difference are reported in Table 1.

Women were older (69 ± 11 vs 63 ± 12, $p < 0.001$) with a higher prevalence of hypertension (80.9% vs 70.1% $p < 0.001$), diabetes mellitus (DM) (36.9% vs 26.9% p < 0.001), impaired kidney function (19.6% vs 16.8%% p < 0.001) and atrial fibrillation (AF) (6.5% vs 5% $p < 0.001$). Women less frequently had smoking habit (26.3% vs 44.9% $p = 0.05$), an history of previous myocardial infarction (MI) (22.4% vs 27.3% $p < 0.001$), previous PCI (27.4% vs 30.5% p < 0.001), previous CABG (8.8% vs 10.9% p < 0.001) and an admission diagnosis of STEMI (24.8% vs 32.5% $p < 0.001$).

Procedural characteristics and baseline pharmacological treatments are reported in Table 2. At angiography, women had less frequently a multivessel disease (MVD) (29.8% vs 36.5% p < 0.001), and bifurcation involved (8.4% vs 9.4% $p = 0.06$), while complete revascularization was less frequently achieved (29.1% vs 33.5% $p < 0.001$).

Echocardiographic data and therapies at discharge are also displayed in Table 2. Women had higher values of left ventricular ejection fraction (LVEF) (51.4% vs 51.1%, $p < 0.001$), despite no difference was found for LVEF <40% in the two group (5.4% vs 5.2%, $p = 0.244$). Regarding medications, Angiotensin converting enzyme inhibitor (ACE-i) or Angiotensin II receptor blocker (ARB) (81.2% vs 76.6%, p < 0.001), statin (93.2% vs 91.7%, $p = 0.001$) and proton-pump inhibitor (PPI) (94.3% vs 92.0%, $p = 0.02$) were more frequently prescribed in male patients, while anti-mineralocorticoid (MRA) (18.2% vs 25.7%, p < 0.001) and diuretic (20.2% vs 32.8%, p < 0.001) in women.

3.2. Endpoints occurrence according to sex

Incidence of both primary and secondary endpoints according to gender is reported in Fig. 1 and women have increased incidence of all three endpoints. Kaplan-Meier analysis of HF hospitalization is reported in Fig. 2 and women showed a statistically higher risk of HF hospitalization compared to men**.** Kaplan-Meier analysis for secondary endpoints according to gender are displayed in Supplementary Fig. 2–3. Women showed a significantly higher risk of HF or CV mortality but not all-cause mortality.

After PSM Kaplan-Meier analysis according to sex showed significantly higher incidence of HF hospitalization in women (Supplementary Fig. 4) and no statistically significant difference was found regarding the composite of HF hospitalization and CV death or all-cause mortality (Supplementary Figs. 5–6).

Independent predictors of secondary endpoints in the overall cohort are displayed in **Supplementary Tables 2–3**. Adjusted predictors HF hospitalization in the overall cohort are reported in **Supplementary Table 4** and among them female sex is associated with increased incidence of primary outcome (HR 1.26; 1.05–1.50; $p = 0.011$).

3.3. Predictors of primary and secondary endpoints according to sex

Independent predictors of both primary and secondary endpoints according to sex are displayed in Table 3 and **Supplementary Tables 4–5.** In women DM (HR 1.96;1.49–2.57; $p < 0.001$), previous or current cancer (HR 2.87;1.84–4.48; p < 0.001), CKD (HR 2.34;1.55–3.54; $p < 0.001$), AF (HR 1.76;1.21–2.54; $p = 0.003$), previous MI (HR 1.46;1.08–1.97; $p = 0.015$ and LVEF lower than 40% (HR

Table 1
Clinical characteristics.

	All Patients (n = 14,699)	Male (n = 10,121)	Female (n = 4578)	P value
Age (years, SD)	65.1 (±11.7)	63.5 (±11.5)	68.6 (±11.4)	< **0.001**
Age ≥ 75 years	3429 (23.3%)	1901 (18.8%)	1528 (33.4%)	< **0.001**
Hyperlipidemia	8654 (58.9%)	5912 (58.4%)	2742 (59.9%)	0.092
Hypertension	10,800 (73.5%)	7095 (70.1%)	3705 (80.9%)	< **0.001**
DM	4416 (30%)	2726 (26.9%)	1690 (36.9%)	< **0.001**
Not ID	3682 (25%)	2218 (21.9%)	1464 (32%)	< **0.001**
ID	1167 (8%)	740 (7.3%)	427 (9.3%)	< **0.001**
Smoking habit				
Current	2806 (19.1%)	2236 (22.1%)	570 (12.5%)	**<0.001**
Previous	2942 (20%)	2308 (22.8%)	634 (13.8%)	**<0.001**
Non-smoker	8950 (60.9%)	5576 (55.1%)	3374 (73.7%)	**<0.001**
COPD (any degree)	781 (5.3%)	563 (5.6%)	218 (4.8%)	**0.048**
PAD	416 (2.8%)	314 (3.1%)	102 (2.2%)	**0.003**
Previous or current cancer	4266 (29.8%)	3173 (37.7%)	1093 (25.2%)	**<0.001**
eGFR with MDRD, ml/min (SD)	80.5 (±22.3)	80.4 (±21.6)	80.7 (±24.0)	**0.360**
eGFR <60 ml/min	2550 (17.7%)	1683 (16.8%)	867 (19.6%)	**<0.001**
Prior Stroke	277 (1.9%)	193 (1.9%)	84 (1.8%)	0.791
Prior Major Bleedings (BARC 3–5)	111 (0.8%)	86 (0.8%)	25 (0.5%)	0.053
Atrial Fibrillation (any grade)	799 (5.5%)	502 (5%)	297 (6.5%)	**<0.001**
Paroxysmal	610 (4.2%)	378 (3.8%)	231 (5.1%)	**0.002**
Persistent	49 (0.3%)	30 (0.3%)	19 (0.4%)	**0.002**
Permanent	140 (1.0%)	93 (0.9%)	47 (1.0%)	**0.002**
Previous MI	3781 (25.7%)	2758 (27.3%)	1023 (22.4%)	**<0.001**
Previous PCI	4333 (29.5%)	3081 (30.5%)	1252 (27.4%)	**<0.001**
Previous CABG	1509 (10.3%)	1106 (10.9%)	403 (8.8%)	**<0.001**
Admission ACS				
STEMI	4332 (30.1%)	3219 (32.5%)	1113 (24.8%)	**<0.001**
NSTEMI	4825 (33.5%)	3301 (33.3%)	1524 (33.9%)	**<0.001**
Unstable Angina	5241 (36.4%)	3388 (34.2%)	1853 (41.3%)	**<0.001**
Hours from symptoms to admission	12.1 (±23.5)	12.2 (±23.2)	12.1 (±24.4)	0.763
Killip ad Admission				
1	13,414 (91.7%)	9264 (91.8%)	4150 (91.5%)	0.984
2	776 (5.3%)	530 (5.3%)	246 (5.4%)	0.984
3	224 (1.5%)	144 (1.4%)	80 (1.8%)	0.984
4	215 (1.5%)	155 (1.5%)	60 (1.3%)	0.984
Grace Score, (SD)	115.8 (±26.2)	114.2 (±26.2)	119.4 (26.0)	**<0.001**
> 141	2043 (13.9%)	1277 (12.6%)	766 (16.7%)	**<0.001**
> 109	8745 (59.5%)	5728 (56.6%)	3017 (65.9%)	**<0.001**
Cardiogenic Shock at Admission	186 (1.3%)	139 (1.4%)	47 (1%)	0.096

SD: standard deviation; ID: insulin-dependent; COPD: chronic obstructive pulmonary disease; PAD: peripheral artery disease; eGFR: estimated glomerular

filtration rate; MDRD: Modification of diet in renal disease; BARC: Bleeding Academic Research Consortium; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction.

3.19;1.91–5.33; $p < 0.001$) were associated with an increased risk of HF hospitalizations while, complete revascularization (HR 0.64;0.42–0.95; $p = 0.027$) and treatment with ACEi/ARBs (HR 0.69;0,49–0.96; $p = 0.029$) resulted protective. In men predictors of HF hospitalizations were DM (HR 1.51;1.21–1.88; $p = 0.001$), previous or current cancer (HR 2.50;1.83–3.41; p < 0.001), CKD (HR 3.57;2.61–4.89; p < 0.001), COPD (HR 2.34;1.70–3.22; p < 0.001), AF (HR 1.95;1.43–2.64; p < 0.001), diuretics therapy at discharge (HR 1.61;1.27–2.04; $p = 0.002$) and LVEF lower than 40% (HR 3.05;2.20–4.24; p < 0.001) were associated with an increased risk of HF hospitalizations while complete revascularization (HR 0.37;0.27–0.46; p < 0.001) was protective. At interaction analysis COPD (p for interaction = 0.026), complete revascularization (p for interaction = 0.003), and ACEi/ARBs therapy at discharge (p for interaction =0.044) showed significant interaction between male and women.

4. Discussion

The aim of the present study is to evaluate incidence and predictors of HF after ACS in a contemporary PCI cohort according to the gender.

The main findings of this sub-analysis of the CORALYS registry are:

1) In our cohort, women with ACS were more frequently older, diabetic, hypertensive and with CKD. The most common cause of admission was unstable angina and at coronary angiography MVD was less frequent compared to men.
2) Women had increased incidence of HF hospitalization, all-cause mortality and composite of CV death and first HF hospitalization after ACS. After adjusting for time and confounding factors, female sex was associated with increased risk of HF hospitalization and with the composite secondary endpoint but not with all-cause mortality.
3) Women and men shared certain predictors of HF (age, DM, history of cancer, CKD, AF, complete revascularization and LVEF), but a significant interaction was observed for COPD, complete revascularization and ACEi/ARBs therapy at discharge.
4) Women less frequently had radial access for PCI, complete revascularization and optimized medical therapy as potent P2Y12 inhibitors, statins, beta-blockers, ACEi/ARBs and MRAs were more prescribed to men patients with possible detrimental effect on patients' prognosis.
5) HF hospitalization after ACS remains an independent predictor of overall mortality

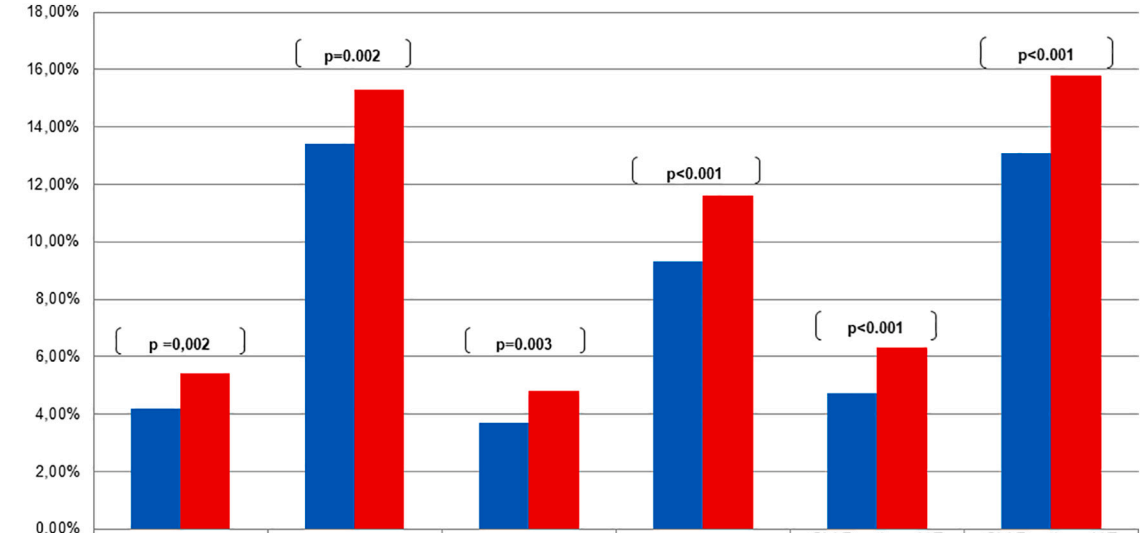
In the last 60 years there has been a trend of reduction in incidence of HF as shown by the Framingham Heart Study, probably due to a more effective primary and secondary prevention strategies and to the availability of early PCI in ACS [1,10]. This reduction is mainly due to a decrease in incidence of HF with reduced LVEF (HFrEF) after myocardial infarction (39.8% to 29.8%) that is, however, partially counterbalanced by an increased incidence of HF with preserved LVEF (HfpEF) (29.0% to 32.6%) [11]. Furthermore, there is also some evidence that HF incidence and mortality decreased more in women compared to men (43% vs 29%) [11], despite similar life-time risk and mortality [12,13].

Moreover, a different distribution of atherothrombotic and HF risk factors due to a distinct hormonal balance in women compared to man that may change both pathophysiology and epidemiology of HF in female patients has been reported. [14,15]. On the other hand, data about long-term outcomes after ACS according to sex are discordant in literature: while some studies reported a higher long-term mortality in women after ACS especially in young patients, other studies reported a higher in-hospital mortality in women, but similar long-term outcomes

Table 2
Procedural characteristics, echocardiographic data and therapies at discharge

	All Patients (n = 14,699)	Male (n = 10,121)	Female (n = 4578)	P value
Vascular Access				
Radial	7408 (51.2%)	5360 (53.8%)	2048 (45.3%)	**<0.001**
Femoral	7066 (48.8%)	4596 (46.2%)	2470 (54.7%)	**<0.001**
Unprotected left main disease	952 (6.5%)	673 (6.6%)	279 (6.1%)	0.219
Multivessel Disease	5054 (34.4%)	3690 (36.5%)	1364 (29.8%)	**<0.001**
Bifurcation involved	1332 (9.1%)	948 (9.4%)	384 (8.4%)	0.059
Complete revascularization	4726 (32.2%)	3395 (33.5%)	1331 (29.1%)	**<0.001**
Before discharge	4580 (31.2%)	3279 (32.4%	1301 (28.4%)	**<0.001**
Planned after discharge	164 (1.0%)	116 (1.1%)	30 (0.7%)	**<0.001**
N° of stents placed (SD)	1.36 (±0.9)	1.38 (±0.9)	1.33 (±0.8)	**0.001**
Need of support before angiography	183 (1.2%)	138 (1.4%)	45 (1%)	0.100
Need of support during PCI	144 (1.0%)	106 (1.0%)	38 (0.8%)	0.097
Need of support after PCI	115 (0.8%)	83 (0.8%)	30 (0.7%)	0.289
Mechanical Complication	82 (0.6%)	59 (0.6%)	23 (0.5%)	**<0.001**
LV volume, ml (SD)	106.6 (±35.1)	112.4 (±34.5)	90.8 (±31.8)	**0.026**
LVEF, %, (SD)	51.3 (±7.5)	51.4 (±7.6)	51.1 (±7.2)	**<0.001**
LVEF<40% (%)	758 (5.2%)	536 (5.4%)	222 (5.2%)	0.244
TAPSE, mm (SD)	16.6 (±9.1)	16.8 (±9.2)	16.0 (±9.0)	0.066
PAPs, mmHg (SD)	32.4 (±11.7)	32.2 (±11.6)	32.9 (11.9)	0.900
Beta-Blockers	12,218 (85.5%)	8430 (85.5%)	3788 (85.4%)	0.879
ACE-i/ARB	10,049 (79.7%)	6978 (81.2%)	3071 (76.6%)	**<0.001**
Statin	12,968 (91.7%)	8998 (93.2%)	3970 (91.7%)	**0.001**
MRAs	1531 (20.3%)	984 (18.2%)	547 (25.7%)	**<0.001**
Diuretic	1469 (23.9%)	876 (20.2%)	593 (32.8%)	**<0.001**
PPI	3249 (93.7%)	2375 (94.3%)	874 (92.0%)	**0.015**
SGLT2 inhibitor	19 (0.3%)	17 (0.4%)	2 (0.1%)	0.313
Glp1 Ras	12 (0.2%)	10 (0.2%)	2 (0.1%)	0.566
DAPT at discharge				
With Clopidogrel	4531 (30.8%)	3033 (30%)	1498 (32.7%)	**<0.001**
With Prasugrel	243 (1.7%)	196 (1.9%)	47 (1%)	**<0.001**
With Ticagrelor	2520 (17.1%)	1960 (19.4%)	560 (12.2%)	**<0.001**
Triple therapy	574 (3.9%)	365 (3.6%)	209 (4.6%)	**0.005**
DOAC	162 (3.9%)	107 (3.7%)	55 (4.2%)	**0.013**
Warfarin	412 (9.8%)	258 (8.9%)	154 (11.7%)	**0.013**

SD: standard deviation; PCI: percutaneous coronary intervention. LVEF: left ventricular ejection fraction at discharge; TAPSE: Tricuspid annular plane systolic excursion; PAPs: systolic pulmonary artery pressure; ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; MRAs: mineralocorticoid receptor antagonists; PPI: proton pump inhibitor; SGLT2: sodium-glucose cotransporter-2; Glp1 ras: glucagon-like peptide 1 receptor antagonist; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant.



	Death at 1 year	Death at the end of FU	HF hospitalization at 1 year	HF hospitalization at the end of FU	CV Death or HF hospitalization at 1 year	CV Death or HF hospitalization at the end of FU
Men	4,20%	13,40%	3,70%	9,30%	4,70%	13,10%
Women	5,40%	15,30%	4,80%	11,60%	6,30%	15,80%

Fig. 1. Incidence of primary and secondary end-points according to sex.
CV: Cardiovascular; HF: heart failure; FU: follow-up.

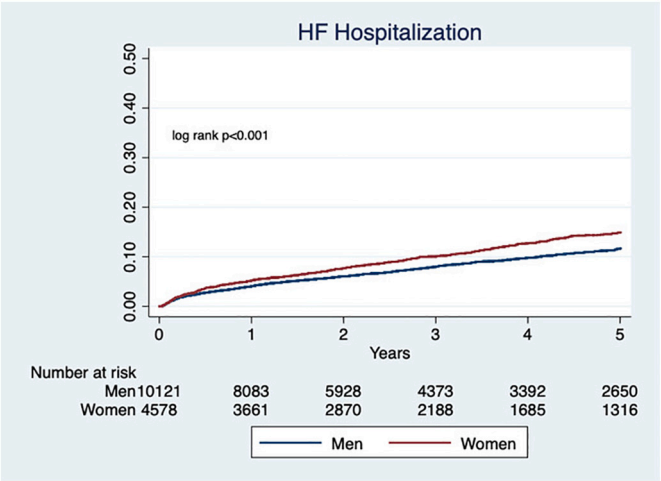


Fig. 2. Freedom from heart failure hospitalization in according to sex.

after hospital discharge [16–18]. Other data suggest a prognostic advantage of female sex after ACS, as showed in both the LADIES ACS study and in Framingham Heart sub-study [19,20]. Recently, the 10-years analysis of the EXAMINATION-EXTENDED trial showed no difference in the primary endpoint (all-cause death, MI, or any revascularization at 10 years) according to sex [21]. Nevertheless, in our study we observed a higher incidence of HF hospitalization and all-cause mortality in women that is confirmed also after adjusting for confounding factors. This discrepancy may be due to the difference between the two cohort, one a selected trial population that enrolled only STEMI patients and one a retrospective, real-world population of consecutive patients with ACS treated with PCI (32.5% males STEMI patients, 24.8% females). Moreover, in the EXAMINATION-EXTENDED study patients were younger than in CORALYS registry (59.8 years vs 63.5 years for males and 67.9 vs 68.6 years for males), less frequently diabetic (17% vs 26.9 in males and 18.1% vs 36.9% in females) and have lower prevalence of multivessel disease (12.6% vs 36.5% in males and 12.2% vs 29.8% in females).

Regarding the incidence of HF hospitalization during the follow-up, the incidence in our cohort (3.7% in males and 4.8% in females) was lower than the one previously reported in previous studies, probably due to improvement in medical therapy optimization after ACS compared to prior data [22,23].

In our cohort both genders shared certain predictors of HF hospitalization, such as age, DM, history of cancer, CKD, AF, complete revascularization and LVEF, that have been highlighted also in previous literature [24–26]. However, some variables appeared to be gender-specific and an interaction between sex and the impact on HF hospitalization was observed for COPD, complete revascularization and treatment with ACEi/ARBs. Nevertheless, these findings need future confirmations but our findings seem to suggest that female gender is an outcome modifier of the relationship between HF hospitalization and other variables.

These differences regarding both patients' characteristics and treatment may help to explain the uncertainty of the prognostic role of gender after ACS that still is a matter of debate, as in the HORIZONS-AMI trial female gender was an independent negative prognostic factor regarding mortality, major bleeding and HF hospitalization [27,28], whereas in the observational population-based Olmsted County study women had lower rates of CV death and HF hospitalizations, despite the inclusion of not only ACS patients [11]. This contrast of previous evidence regarding the impact of gender on HF hospitalization and our findings of certain gender-specific predictors point out the need of further balanced studies to achieve a gender-specific management of ACS patients due to the possible detrimental role of female sex relative to HF with different weight of certain characteristics in male or women as shown in the CORALYS cohort.

However, our study also points out the inequalities regarding different access to radial PCI, complete revascularization and optimized medical therapy, all more frequent in men than in women in CORALYS cohort. Similar discrepancies were found also in a large European registry that showed lower rate of primary PCI and evidence-based drugs such as beta-blockers, ACEi/ARBs and statins [29]. These aspects highlight that despite the effort to provide equal care to men and women certain inequalities still exist and that there is room to improve ACS

Table 3
Independent predictors of heart failure hospitalization according to sex

	In female gender		In male gender		P for interaction
	HR; 95% CI	P value	HR; 95% CI	P value	P value
Age ≥ 75	1.18; 0.86–1.62	0.316	0.86; 0.65–1.15	0.304	0.191
Hypertension	1.07; 0.73–1.57	0.732	1.17; 0.91–1.51	0.224	0.992
Diabetes	**1.96; 1.49–2.57**	**<0.001**	**1.51;1.21–1.88**	**0.001**	0.307
Smoking	0.97; 0.71–1.32	0.843	1.01; 0.81–1.25	0.939	0.268
Previous or current cancer	**2.87; 1.84–4.48**	**<0.001**	**2.50; 1.83–3.41**	**<0.001**	0.581
eGFR<60 ml/min	**2.34; 1.55–3.54**	**<0.001**	**3.57; 2.61–4.89**	**<0.001**	0.689
Peripheral artery disease	0.72; 0.38–1.34	0.297	1.29; 0.88–1.90	0.192	0.113
Chronic obstructive pulmonary disease	0.16; 0.68–1.97	0.594	**2.34; 1.70–3.22**	**<0.001**	**0.026**
Atrial fibrillation	**1.76; 1.21–2.54**	**0.003**	**1.95;1.43–2.64**	**<0.001**	0.871
Previous myocardial infarction	**1.46; 1.08–1.97**	**0.015**	1.18;0.95–1.48	0.143	0.516
STEMI at admission	0.83; 0.60–1.15	0.260	1.10; 0.88.1.39	0.402	0.179
GRACE score > 141	1.35; 0.97–1.87	0.076	1.21; 0.91–1.61	0.188	0.478
Radial access	0.97; 0.69–1.36	0.848	1.16; 0.92–1.58	0.214	0.144
ULM or Multivessel disease	1.00; 0.76–1.31	0.981	0.94; 0.76–1.17	0.592	0.954
Complete revascularization	**0.63; 0.42–0.95**	**0.027**	**0.37; 0.27–0.46**	**<0.001**	**0.003**
Beta-blockers at discharge	0.67; 0.44–1.00	0.050	0.90; 0.65–1.29	0.534	0.830
ACEi/ARB at discharge	**0.69; 0.49–0.96**	**0.029**	1.03; 0.78–1.36	0.835	**0.044**
Diuretics at discharge	1.24; 0.93–1.65	0.143	**1.61; 1.27–2.04**	**<0.001**	0.371
Left ventricular ejection fraction <40 at discharge	**3.19; 1.91–5.33**	**<0.001**	**2.27; 1.58–3.25**	**<0.001**	0.456

HR: hazard ratio; CI: confidence interval; eGFR: estimated glomerular filtration rate; STEMI: ST-elevation myocardial infarction; ULM: unprotected left main; ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers.

patients care [30].

Finally, women are often underrepresented in ACS and HF clinical trial because of a lower prevalence of CVD compared with men and even in latest years in which this concern seems to be a hot topic, especially in secondary prevention and HF prevention, trials concerning CAD and HF continue to report a proportionally low percentage of women participants despite known physiological and pathophysiological differences.

Thus, there is a strong clinical need that future randomized studies both in ACS and HF will enroll more frequently women and investigate the impact of gender in ACS patients and in HF development in order to provide a tailored treatment and secondary prevention programs in women [31,32].

The present study has some limitations. First, it is a retrospective study and although multivariate adjustment was performed, potential bias coming from unmeasured variables or confounding factors cannot be excluded. Second, the fact that this is a multicenter and international registry may be influenced by differences in operators' experience, common clinical practice and by improvements in PCI materials and techniques.

5. Conclusion

After ACS, women showed an increased risk of re-admission for HF which remained significant after multivariable adjustment. Moreover, the prognostic weight of certain predictors seems to be different between male and female patients, highlighting that gender may be an outcome modifier of the relationship between a covariate and HF hospitalization. Furthermore, our registry points out the inequality regarding to access to optimized treatment.

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None.

Authors' contributions

Concept and design of the study: EE, FDA, GMDF. Data analysis: EE, FB. Data acquisition: GC, WW, SL, MM, SRR, EF, GG, AT, ODF, GG, GM, AB, DM, ZH, NG, AI, BG, ING, FU, MB, LB, FM, PD, CM, MM, NM, MS, MG, GC, WW, EAA, GS. Drafting of the manuscript: EE, FB, FDA. Revising of the manuscript: ODF, IP, GS, WW, GC. Final approval of the manuscript: FDA, GMDF.

Declaration of Competing Interest

None.

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None.

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