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CLINICAL INVESTIGATIONS

Influence of sex and pregnancy on survival in patients admitted with heart failure: Data from a prospective multicenter registry

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Background: Female sex is an independent predictor of better survival in patients with heart failure (HF), but the mechanism of this association is unknown. On the other hand, pregnancies have a strong influence on the cardiovascular system.

Hypothesis: Sex and previous gestations might have a prognostic impact on 1-year mortality in patients admitted with HF.

Methods: We conducted an observational, prospective, consecutive, multicenter registry of 1831 patients (756 females [41.2%]) admitted with HF.

Results: Females had a more advanced age (75.2 ±11.4 vs 70.4 ±12.2 years), less ischemic heart disease (167 [25.3%] vs 446 [47.3%]), and higher left ventricular ejection fraction (52.0% ±16.6% vs 41.1% ±17.0%) than did men (all *P* values <0.001). During 1-year follow-up, 373 (20.4%) patients died (151 females and 222 males). Female sex was an independent predictor for survival (hazard ratio: 0.79, 95% confidence interval: 0.64–0.98, *P* = 0.03). In 504 women (65.9%), the exact number of previous pregnancies could be determined; 62 women (12.3%) had no previous pregnancies, 288 (57.1%) women had 1 or 2 pregnancies, and 154 women (30.6%) had ≥3 pregnancies. We found an association between the number of previous gestations and better survival (hazard ratio: 0.878, 95% confidence interval: 0.773–0.997, *P* = 0.045).

Conclusions: In patients admitted with HF, female sex and the number of previous pregnancies are independently associated with better 1-year survival.

KEYWORDS

Heart Failure, Pregnancy, Prognosis, Sex

1 | INTRODUCTION

Sex-related differences in heart failure (HF) patients are well known, and female sex is an independent predictor of better survival in this population.[1–4] However, the reasons for this better prognosis are unknown. More than 10 years ago, we hypothesized that previous pregnancies could play a role by conditioning the heart toward a better accommodation to cardiac dysfunction.[5] However, pregnancies have been recently described as deleterious for the cardiovascular (CV) system, not only in the case of pathological pregnancies,[6] but also in normal ones.[7–10] On the other hand, other data support that pregnancy could have a positive CV influence, as the hemodynamic changes observed during gestation are comparable with those seen in sportspersons.[11,12] Moreover, fetal microchimerism during pregnancy could favor some degree of heart regeneration.[13] In addition, a beneficial long-term CV influence of the pregnancy-associated hormone relaxin in patients with HF has been suggested.[14] Although there are no previous reports analyzing the influence of pregnancy on prognosis in HF patients, Chieffo et al[15] found recently that, in women undergoing transcatheter aortic valve replacement, a history of pregnancy was associated with better prognosis. Our aim was to study prospectively the influence of sex and pregnancy on 1-year mortality in a large sample of patients admitted with HF.

2 | METHODS

2.1 | Study population

The study population consists of 1831 patients with acute HF admission enrolled in the Spanish Network for the Study of Heart Failure II (REDINSCOR II Registry). This is a prospective, multicenter study designed to describe the clinical profile of patients with HF in Spain and to assess predictors of prognosis. Patients were consecutively recruited between November 2013 and November 2014 in 19 hospitals. A maximum number of 200 patients was permitted per center. Inclusion criteria were (1) age > 18 years and (2) hospitalization for HF (>24 h) in a cardiology department. Patients were treated according to current guidelines in those years.[16] Exclusion criteria were (1) HF due to ST-segment elevation acute coronary syndrome or (2) concomitant terminal disease.

The study complies with the Declaration of Helsinki, and the registry was approved by the ethics committees of each participating center. All patients gave written informed consent.

2.2 | Study variables

Data were collected using specifically designed web forms (http://www.redinscor2.org), and quality controls were undertaken regularly. We recorded the following clinical variables at study inclusion: (1) demographic and clinical history; (2) physical examination; (3) chest radiography; (4) electrocardiogram, laboratory blood test, and echocardiography at admission and before discharge; and (5) medical treatment. Standard criteria were used to define each variable. The number of pregnancies was a prespecified research question in women.

2.3 | Follow-up

Follow-up data were obtained by telephone contact at 1, 3, 6, and 12 months after discharge and from the event reports entered in the electronic records of each hospital. Patients lost to follow-up (30 [1.6%]) were censored in the survival analysis.

2.4 | Statistical analysis

Continuous variables are expressed as mean ±SD or as median (interquartile range) whenever appropriate. Differences in continuous variables were tested by analysis of variance or Student *t* test for independent samples. Categorical variables are presented as frequencies and percentages. Differences in the categorical variables were assessed by the χ^2 test or by Fisher exact test. The study endpoint for all regression analyses was the date of death at 1 year of follow-up. To achieve our first objective, a multivariate analysis (Cox regression model), including clinical meaningful variables and all possible

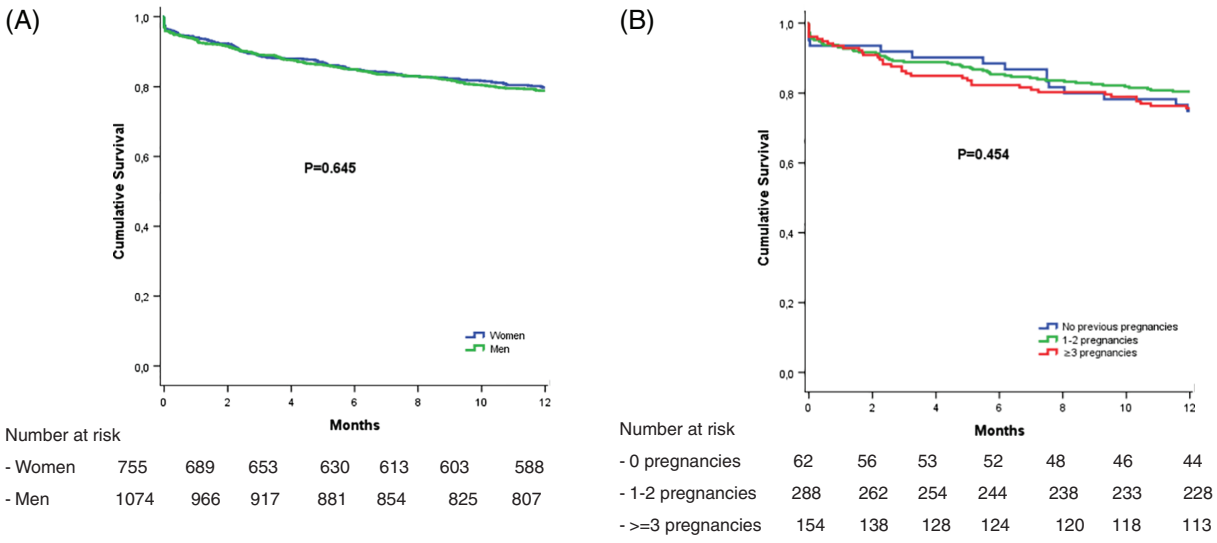

FIGURE 1 (A) Cumulative survival in 1075 men and 756 women and (B) cumulative survival in 504 women according to the number of previous pregnancies

TABLE 1 Sex-related differences in the clinical profile of 1831 patients admitted with HF in cardiology departments

	Females, n = 756 (41.2%)	Males, n = 1075 (58.7%)	*P* Value
Mean age, y	75.2 ± 11.4	70.4 ±12.2	<0.001
Previous CV admissions	1 (0–2)	1 (0–3)	0.011
Etiology			<0.001
Ischemic	167 (25.3)	446 (47.3)	
Valvular	233 (35.3)	178 (18.9)	
HTN	146 (22.1)	110 (11.7)	
Idiopathic	55 (8.3)	144 (15.3)	
Other	59 (8.9)	65 (7.0)	
Follow-up			<0.001
Only general practitioner	298 (40.1)	367 (34.8)	
Cardiologist	377 (50.7)	534 (50.6)	
HF unit	46 (6.2)	128 (12.1)	
Other specialist	23 (3.1)	26 (2.5)	
Tobacco consumption			<0.001
No	654 (86.5)	349 (32.6)	
Previous	71 (9.4)	559 (52.2)	
Active	31 (4.1)	162 (15.1)	
Alcohol consumption	11 (1.5)	182 (17.1)	<0.001
COPD	61 (8.1)	229 (21.5)	<0.001
OSA	58 (7.8)	135 (12.7)	0.001
PAD	70 (9.4)	140 (13.3)	0.011
MI	144 (19.4)	340 (32.7)	<0.001
Syncope	27 (3.6)	91 (8.6)	<0.001
Pregnancies	2 (1–3)	—	—
Medications			
ACEIs	256 (34.1)	432 (40.4)	0.006
ARBs	206 (27.6)	238 (22.6)	0.015
β-Blockers	399 (52.8)	597 (55.3)	0.005
Ivabradine	22 (2.9)	65 (6.1)	0.002
Statins	384 (51.1)	610 (57.0)	0.012
Aldosterone antagonists	164 (21.5)	283 (25.8)	<0.001
Nitrates	85 (11.3)	178 (16.7)	0.001
ASA	225 (29.8)	412 (38.5)	<0.001
Clopidogrel	63 (8.3)	134 (12.5)	0.005
Anticoagulation	326 (43.2)	394 (36.8)	0.006
Cardiac resynchronization	13 (1.7)	38 (3.6)	0.020
ICD	20 (2.7)	107 (10.0)	<0.001
NYHA classification			0.002
I	138 (20.0)	276 (27.6)	
II	445 (64.4)	605 (60.5)	
III	105 (15.2)	115 (11.5)	
IV	3 (0.4)	4 (0.4)	
Cardiac precipitating factors			0.002
None	319 (42.4)	487 (45.5)	
AF	157 (20.9)	159 (14.9)	
Supraventricular arrhythmia	16 (2.1)	9 (0.8)	
VT	3 (0.4)	7 (0.7)	
Bradycardia	19 (2.5)	22 (2.1)	
NSTE-ACS	35 (4.7)	73 (6.8)	
Other	203 (27.0)	313 (29.3)	
Noncardiac precipitating factors			0.002
None	554 (76.1)	744 (72.5)	
Noncompliance	16 (2.2)	43 (4.2)	

confounding factors with a *P* value <0.2, was built to assess the influence of sex on survival in the complete cohort. A backward stepwise method was used to identify independent risk predictors with $P < 0.05$ for the inclusion or deletion criterion. The proportionality assumption of the models was verified using time-dependent variables. Finally, a reduced model was obtained if magnitude change in the hazard ratios (HR) was <10% in the main variable when removing possible confounding factors. Secondly, the same methodology was employed to analyze the influence of the number of previous pregnancies on survival in the subgroup of women. A regression multiple imputations (n = 15) was applied whenever necessary (missing data range, 0%–25%), except for N-terminal pro brain natriuretic peptide, where the missing data were recoded as "nonmeasured" and were analyzed as such, because a "nonmeasured" N-terminal pro brain natriuretic peptide can be potentially associated to the events.[17–19]

All analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY) and Stata version 13.1 (StataCorp LP, College Station, TX).

3 | RESULTS

We included 1831 patients (756 women [41.2%]). The main sex-related differences in baseline clinical profile are depicted in Table 1. Women had a more advanced age; less frequent ischemic heart disease, obstructive sleep apnea, and peripheral arterial disease; and lower tobacco/alcohol consumption than men. Women presented more frequently a functional class >I, but they received drugs less frequently than did men, except for angiotensin receptor blockers. Cardiac resynchronization therapy and implantable cardioverter-defibrillators were also less frequently used in women than in men, but women presented systolic dysfunction less frequently. Also, the rate of cardiac and noncardiac precipitating factors was different between the sexes, as were the symptoms and signs. During 1-year follow-up, 373 (20.4%) patients died (151 women [20.0%] and 222 men [20.7%]; Figure, 1A). Female sex was an independent predictor for all-cause mortality (HR: 0.79, 95% CI: 0.64–0.98; Table 2). In 504 women (65.9%), the exact number of previous pregnancies could be determined; 62 women (12.3%) had no previous pregnancies, 288 (57.1%) women had 1 or 2 pregnancies, and 154 women (30.6%) had ≥3 pregnancies. The main differences between the clinical profile and 1-year mortality of these 3 groups are depicted in Table 3. Women without previous pregnancies had a more favorable clinical profile, as they were younger, presented less frequently with ischemic etiology, and had a lower prevalence of diabetes and hypertension than did women with previous pregnancies (survival curves according to number of previous gestations are depicted in Figure, 1B). For variables associated with mortality in women during the first year, see Supporting Information, Appendix, in the online version of this article (univariate analysis). When adjusted by all the independent predictors of mortality, we found an association between the number of previous pregnancies and a better survival (HR: 0.878, 95% CI: 0.773–0.997; Table 4).

TABLE 2 Independent predictors of mortality during the first year in 1831 patients admitted with HF in cardiology departments

	HR (95% CI)	*P* Value
Female sex	0.79 (0.64–0.98)	0.03
Age, y	1.02 (1.01–1.03)	0.005
Functional class >I	1.54 (1.12–2.12)	0.007
SBP, mm Hg	0.992 (0.988–0.995)	<0.001
BMI, kg/m^2	0.975 (0.954–0.996)	0.02
Barthel ADL index	0.98 (0.98–0.99)	<0.001
GFR, mL/min/1.73 m^2	0.98 (0.98–0.99)	<0.001
NT-proBNP ≥1500 ng/L	1.85 (1.21–2.83)	0.004
Nonmeasured NT-proBNP	2.00 (1.28–3.13)	0.002

Abbreviations: ADL, activities of daily living; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro brain natriuretic peptide; SBP, systolic blood pressure.

4 | DISCUSSION

This study reveals that female sex and the number of previous pregnancies are associated with better 1-year survival in patients admitted with HF.

TABLE 1 (Continued)

	Females, n = 756 (41.2%)	Males, n = 1075 (58.7%)	*P* Value
Infection	65 (8.9)	130 (12.7)	
NSAIDs	18 (2.5)	11 (1.1)	
Other	75 (10.3)	98 (9.6)	
Symptoms and signs			
Paroxysmal nocturnal dyspnoea	323 (44.9)	529 (51.5)	0.007
Third heart sound	50 (6.8)	115 (11.2)	0.002
Hepatomegaly	89 (12.1)	192 (18.4)	<0.001
LVEF, %	52.0 ± 16.6	41.1 ± 17.0	<0.001
NT-proBNP, ng/L	444.4 (201.1–888.5)	532.0 (248.0–1064.0)	0.004

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid (aspirin); COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; OSA, obstructive sleep apnea; PAD, peripheral arterial disease; SD, standard deviation; VT, ventricular tachycardia. Data are presented as n (%), mean ± SD, or median (IQR).

TABLE 3 Differences related to number of previous pregnancies in the clinical profile of 504 women admitted with HF in cardiology departments[a]

No. of Pregnancies	0, n = 62	1–2, n = 288	≥3, n = 154	Unknown, n = 252	*P* Value
Mean age, y	67.2 ±16.6	75.7 ±10.7	75.8 ±10.1	76.3 ±10.7	<0.001
Etiology					0.001
Ischemic	7 (14.0)	73 (29.7)	41 (30.1)	46 (20.2)	
Valvular	18 (36.0)	83 (33.7)	40 (29.4)	92 (40.4)	
Idiopathic	9 (18.0)	15 (6.1)	15 (11.0)	16 (7.0)	
Hypertrophic	2 (4.0)	8 (3.3)	3 (2.2)	14 (6.1)	
HTN	9 (18.0)	61 (24.8)	30 (22.1)	46 (20.2)	
Other	5 (10.0)	6 (2.4)	7 (5.1)	8 (3.5)	
Tobacco consumption					<0.001
No	41 (66.1)	251 (87.2)	140 (90.9)	222 (88.1)	
Previous	13 (21.0)	23 (8.0)	10 (6.5)	25 (9.9)	
Active	8 (12.9)	14 (4.9)	4 (2.6)	5 (2.0)	
DM	25 (40.3)	145 (50.5)	93 (60.8)	96 (38.1)	<0.001
HTN	41 (66.1)	233 (81.2)	130 (85.0)	190 (76.0)	0.009
MI	6 (9.7)	65 (22.6)	40 (26.5)	33 (13.6)	0.001
Mean eGFR (CKD-EPI), mL/min/1.73m^2	67 ± 28	58 ± 23	53 ± 26	57 ± 23	0.002
NT proBNP ≥1500 ng/L	27 (71.1)	167 (80.3)	90 (72.9)	144 (79.1)	0.280
Mean Barthel ADL index score	89 ± 20	88 ±21	81 ±25	87 ±25	0.017
Mortality during the first year	15 (24.2)	56 (19.4)	37 (24.0)	43 (17.1)	0.301

Abbreviations: ADL, activities of daily living; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; SD, standard deviation. Data are presented as n (%) or mean ± SD.

[a] Data previous to hospitalization.

In HF patients, the association of female sex with prognosis has been previously described.[1–4] Women with HF are usually older and have a different clinical profile with respect to men, and most of the differences we found, including the lower prevalence of ischemic heart disease and systolic dysfunction, have been already reported. Although the absence of these 2 conditions has been related to a better prognosis in HF patients,[20] the superior survival of females with respect of males also occurs in patients with ischemic HF[4] and irrespective of left ventricular ejection fraction,[2] suggesting the presence of a female sex-specific protector factor.[3]

The influence of the number of previous pregnancies in women with HF has not been previously reported. We found that women with absence of previous pregnancies presented apparently the best prognosis; however, this was determined by their better clinical profile. Although a possible deleterious effect of pregnancy on the CV system has been recently described in the case of pathological pregnancies,[6] and in normal ones,[7–10] our data do not support this hypothesis. The changes in the CV system are complex, and some of them could have a negative influence, such as maladaptation to chronic volume overload and impaired myocardial relaxation,[7] alteration of left ventricular (LV) contractility and function,[8,9] and decrease of the carotid artery elasticity.[21] Pregnancy entails an important stress to the heart, with an increase in the heart rate, ventricular volumes, cardiac output, and ventricular hypertrophy[11]; and some of these factors, such as heart rate[22] or ventricular hypertrophy,[23] have been related to poor prognosis in HF patients. However, in our view, beneficial pregnancy-related changes are more frequent and more relevant; these include the decline in vascular resistance,[11] related, in part, to the increase of atrial natriuretic peptide[24] and relaxin.[25] In fact, the positive long-term CV influence of serelaxin has been suggested.[14] Moreover, the presence of XY cardiomyocytes in the hearts of women who have had male children has been reported,[13] and this microchimerism could produce some degree of rejuvenation during pregnancy.

TABLE 4 Independent predictors of mortality during the first year in 504 women admitted with HF in cardiology departments

	HR (95% CI)	*P* Value
GFR, mL/min/1.73 m^2	0.979 (0.970–0.988)	<0.001
NT-proBNP ≥1500 ng/L	2.397 (1.207–4.763)	0.014
Barthel ADL index	0.980 (0.973–0.986)	<0.001
No. of previous pregnancies	0.878 (0.773–0.997)	0.045

Abbreviations: ADL, activities of daily living; CI, confidence interval; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro brain natriuretic peptide.

Our data support the beneficial effect of previous pregnancies in women admitted with HF, as the number of previous gestations was an independent predictor of better survival. A greater number of pregnancies could result in cardiac preconditioning, making these women more resistant to adverse LV remodeling and HF later in life. In sum, there are several pregnancy-related CV effects, and our results suggest that the final balance is a positive one, although we would like to stress the need to perform further work specifically designed to evaluate the long-term influence of pregnancy in women with heart disease. Broader studies regarding other female sex-related variables and HF would be welcome. In fact, early age at menopause recently has been associated with a greater risk of HF[26]; changes in gene

expression in the pregnant heart in animal models have been described[27]; sex-biased miRNA networks may explain sex-specific CV pathophysiologies in women[28]; and reverse remodeling is more frequent among women, regardless of cause and severity of LV dysfunction.[29]

4.1 | Study limitations

Our study has some limitations. In a large number of women (252 [33%]), the exact number of previous pregnancies could not be determined. In addition, the number of women with no previous pregnancies was relatively low (62). Finally, our data were obtained from patients admitted to cardiology departments due to HF and may not be extrapolated to other populations. However, this is the first description regarding the possible effect of previous pregnancies in the prognosis of HF, and our study was specifically designed to test this effect.

5 | CONCLUSION

In patients admitted with HF, female sex was independently associated with better survival. In women, the number of previous pregnancies was related to better prognosis.

Conflicts of interest

The authors declare no potential conflicts of interest.

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REFERENCES

1. Martínez-Sellés M, García Robles JA, Prieto L, et al. Systolic dysfunction is a predictor of long term mortality in men but not in women with heart failure. *Eur Heart J*. 2003;24:2046–2053.
2. O'Meara E, Clayton T, McEntegart MB, et al; CHARM Investigators. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Circulation*. 2007;115:3111–3120.
3. Martínez-Sellés M, Doughty RN, Poppe K, et al; Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). Gender and survival in patients with heart failure: interactions with diabetes and aetiology: results from the MAGGIC individual patient meta-analysis. *Eur J Heart Fail*. 2012;14:473–479.
4. Dunlay SM, Roger VL. Gender differences in the pathophysiology, clinical presentation, and outcomes of ischemic heart failure. *Curr Heart Fail Rep*. 2012;9:267–276.
5. Martínez-Sellés M, Muñoa MD, Martínez E, et al. The influence of sex on right ventricular dysfunction in patients with severely depressed left ventricular ejection fraction. *Eur J Heart Fail*. 2006;8:400–403.
6. Cain MA, Salemi JL, Tanner JP, et al. Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes. *Am J Obstet Gynecol*. 2016;215:484.e1–484.e14.
7. Melchiorre K, Sharma R, Khalil A, et al. Maternal cardiovascular function in normal pregnancy: evidence of maladaptation to chronic volume overload. *Hypertension*. 2016;67:754–762.
8. Estensen ME, Beitnes JO, Grindheim G, et al. Altered maternal left ventricular contractility and function during normal pregnancy. *Ultrasound Obstet Gynecol*. 2013;41:659–666.
9. Geva T, Mauer MB, Striker L, et al. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *Am Heart J*. 1997;133:53–59.
10. Sanghavi M, Kulinski J, Ayers CR, et al. Association between number of live births and markers of subclinical atherosclerosis: the Dallas Heart Study. *Eur J Prev Cardiol*. 2016;23:391–399.
11. Robson SC, Hunter S, Boys RJ, et al. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol*. 1989;256(4 part 2):H1060–H1065.
12. Martínez-Sellés M. What do women have in their hearts [article in Spanish]? *Rev Esp Cardiol*. 2007;60:1118–1121.
13. Bayes-Genis A, Bellosillo B, de la Calle O, et al. Identification of male cardiomyocytes of extracardiac origin in the hearts of women with male progeny: male fetal cell microchimerism of the heart. *J Heart Lung Transplant*. 2005;24:2179–2183.
14. Teerlink JR, Cotter G, Davison BA, et al; RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet*. 2013;381:29–39.
15. Chieffo A, Petronio A, Mehilli J, et al; WIN-TAVI Investigators. Acute and 30-day outcomes in women after TAVR: results from the First Women in Transcatheter Aortic Valve Implantation (WIN-TAVI) real-world registry. *JACC Cardiovasc Interv*. 2016;9:1589–1600.
16. McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. 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 [published correction appears in *Eur Heart J*. 2013;34:158]. *Eur Heart J*. 2012;33:1787–1847.
17. Núñez E, Steyerberg EW, Núñez J. Regression modeling strategies [article in Spanish]. *Rev Esp Cardiol*. 2011;64:501–507.
18. Haukoos JS, Newgard CD. Advanced statistics: missing data in clinical research—part 1: an introduction and conceptual framework. *Acad Emerg Med*. 2007;14:662–668.
19. Little R, Rubin D. Statistical analysis with missing data. *J Educ Stat*. 1991;16:150–155.
20. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*. 2012;33:1750–1757.
21. Kärkkäinen H, Saarelainen H, Valtonen P, et al. Carotid artery elasticity decreases during pregnancy—the Cardiovascular Risk in Young Finns study. *BMC Pregnancy Childbirth*. 2014;14:98.
22. Hamill V, Ford I, Fox K, et al. Repeated heart rate measurement and cardiovascular outcomes in left ventricular systolic dysfunction. *Am J Med*. 2015;128:1102–1108.
23. Otaki Y, Takahashi H, Watanabe T, et al. Electrocardiographic left ventricular hypertrophy Cornell product is a feasible predictor of cardiac prognosis in patients with chronic heart failure. *Clin Res Cardiol*. 2014;103:275–284.
24. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstet Gynecol Surv*. 1994;49(12 suppl):S1–S14.
25. Conrad KP, Novak J. Emerging role of relaxin in renal and cardiovascular function. *Am J Physiol Regul Integr Comp Physiol*. 2004;287:R250–R261.
26. Appiah D, Schreiner PJ, Demerath EW, et al. Association of age at menopause with incident heart failure: a prospective cohort study and meta-analysis. *J Am Heart Assoc*. 2016;5:e003769.
27. Chung E, Leinwand LA. Pregnancy as a cardiac stress model. *Cardiovasc Res*. 2014;101:561–570.
28. Florijn BW, Bijkerk R, van der Veer EP, et al. Gender and cardiovascular disease: are sex-biased miRNA networks a driving force behind heart failure with preserved ejection fraction in women? *Cardiovasc Res*. 2018;114:210–225.

29. Aimo A, Vergaro G, Castiglione V, et al. Effect of sex on reverse remodeling in chronic systolic heart failure. *JACC Heart Fail*. 2017;5: 735–742.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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