ESC European Society of Cardiology

European Journal of Preventive Cardiology (2021) **28**, 1711–1719
doi:10.1093/eurjpc/zwab078

FULL RESEARCH PAPER

Sex differences on new-onset heart failure in patients with known or suspected coronary artery disease

Julio Núñez [1,2,3,4†], Miguel Lorenzo [1,2†], Gema Miñana [1,2,3,4], Patricia Palau [1,2,4], Jose V. Monmeneu [5], Maria P. López-Lereu [5], Jose Gavara [2,6], Victor Marcos-Garcés[1,2], Cesar Ríos-Navarro [2], Nerea Pérez [2], Elena de Dios [3], Eduardo Núñez [1], Juan Sanchis [1,2,3,4], Francisco J. Chorro [1,2,3,4], Antoni Bayés-Genís [3,7], and Vicent Bodí[1,2,3,4]*

[1]Cardiology Department, Hospital Clínico Universitario de Valencia, Av. Blasco Ibañez, 17, 46010, Valencia, Spain; [2]Instituto de Investigación Sanitaria INCLIVA, Menéndez y Pelayo, 4, 46010, Valencia, Spain; [3]Centro de Investigación Biomédica en Red - Cardiovascular (CIBER-CV), Av. Monforte de Lemos, 3-5, 28029 Madrid, Spain; [4]Department of Medicine, Faculty of Medicine and Odontology, University of Valencia, Av. de Blasco Ibáñez, 15, 46010 Valencia, Spain; [5]Cardiovascular Magnetic Resonance Unit, Exploraciones Radiológicas Especiales (ERESA), Colón, 1, 46004 Valencia, Spain; [6]Center for Biomaterials and Tissue Engineering, Universitat Politècnica de València, Camino de Vera s/n, 46022 Valencia, Spain; and [7]Cardiology Department, Hospital Universitari Germans Trias i Pujol, Carretera de Canyet, s/n, 08916, Badalona, Spain

Received 3 February 2021; revised 3 April 2021; editorial decision 20 April 2021 ; online publish-ahead-of-print 10 May 2021

Aims The impact of sex in patients with CAD has been widely reported, but little is known about the influence of sex on the risk of new-onset HF in patients with known or suspected CAD. We aimed to examine sex-related differences and new-onset heart failure (HF) risk in patients with known or suspected coronary artery disease (CAD) undergoing vasodilator stress cardiac magnetic resonance (CMR).

Methods and results We prospectively evaluated 5899 consecutive HF-free patients submitted to stress CMR for known or suspected CAD. Ischaemic burden (number of segments with stress-induced perfusion deficit) and left ventricular ejection fraction (LVEF) were assessed by CMR. The association between sex and new-onset HF (including outpatient diagnosis or acute HF hospitalization) was evaluated using a Cox proportional hazards regression model adjusted for competing events [death, myocardial infarction (MI), and revascularization]. A total of 2289 (38.8%) patients were women. During a median follow-up of 4.5 years, 610 (10.3%) patients died, 191 (3.2%) suffered an MI, 905 (15.3%) underwent revascularization, and 314 (5.3%) developed new-onset HF. Unadjusted new-onset HF rates were higher in women than in men (1.25 vs. 0.83 per 100 person-years, $P = 0.001$). After comprehensive multivariate adjustment, women showed an increased risk of new-onset HF (hazard ratio 1.58, 95% confidence interval 1.18–2.10; $P = 0.002$). We found a sex-differential effect along the continuum of LVEF (P-value for interaction = 0.007). At lower LVEF, there was an increased risk in both sexes. However, compared with men, the risk of new-onset HF was higher in women with LVEF >55%.

Conclusion Women with known or suspected CAD are at a higher risk of new-onset HF. Further studies are needed to unravel the mechanisms behind these sex-related differences.

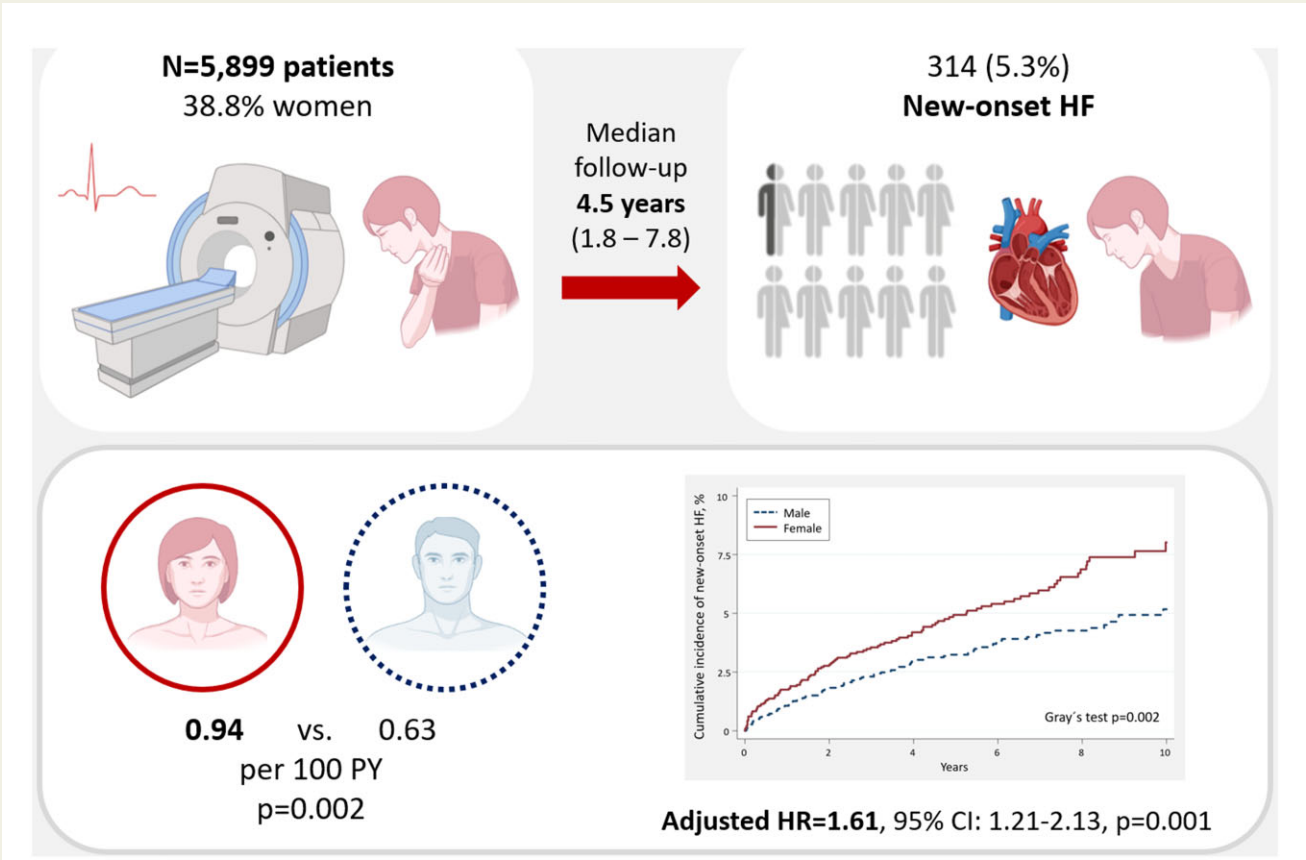
* Corresponding author. Tel: +34 96 1973500, Fax: +34 96 1973979, Email: vicente.bodi@uv.es

† The first two authors contributed equally to the study.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2021. For permissions, please email: journals.permissions@oup.com.

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

Graphical Abstract



Keywords Cardiac magnetic resonance • Coronary artery disease • Sex • Heart failure

Introduction

Several reports have outlined differences in clinical characteristics, pathophysiology, and outcomes between men and women with coronary artery disease (CAD).[1–6] Most prognostic studies have focused on the risk of mortality, recurrent myocardial infarction (MI), or revascularization after MI. Despite sex differences in age, comorbidities, and treatments in the setting of acute coronary syndromes, some studies have pointed to a significantly increased risk of heart failure (HF) in women.[7,8] However, little is known about the impact of sex on new-onset HF patients with ambulatory known or suspected CAD.

In this study, we sought to evaluate sex-related differences and risk of new-onset HF in a cohort of patients who underwent vasodilator stress cardiac magnetic resonance (CMR) imaging. Additionally, we aimed to analyse the influence of CMR ischaemic burden, and CMR left ventricular systolic function on new-onset HF risk across both sexes.

Methods

Study population

This study was based on a large prospective registry that included 6675 consecutive patients referred for vasodilator stress CMR for known or suspected CAD from 2001 to 2016.[9–11] Baseline characteristics and CMR data were prospectively recorded and immediately entered into the predefined database. The physician in charge of the patient had full access to all CMR parameters, and the patients' management was left to their discretion. After excluding cases with incomplete baseline data, those lost to follow-up, cardiomyopathy, incomplete CMR study, insufficient image quality, and prior diagnosis of HF, there were 5899 patients finally included in this analysis (*Figure 1*).

This registry was carried out following the Declaration of Helsinki, and all patients provided signed consent. In September 2018, the local ethics committee authorized a retrospective update of the occurrence of all-cause mortality.

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

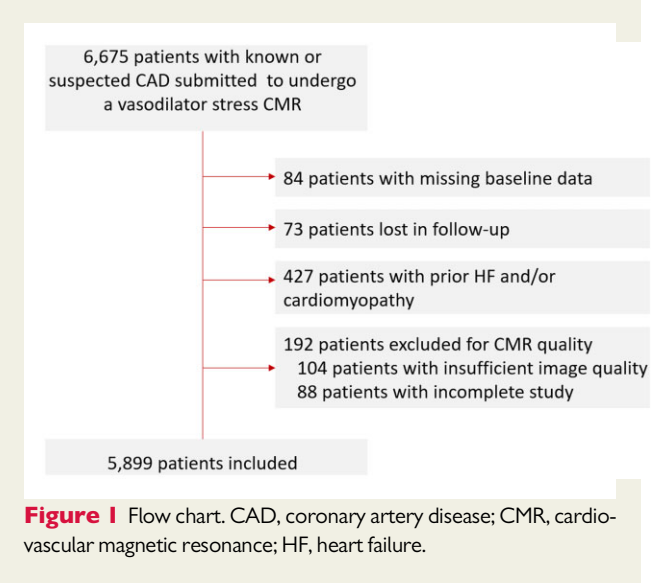


Figure 1 Flow chart. CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; HF, heart failure.

Cardiac magnetic resonance data analysis

Technical aspects related to CMR studies are depicted in Supplementary material online, *File S1* and elsewhere.[9,10,12] Images were examined using customized software (Syngo, Siemens, Erlangen, Germany).

Left ventricular end-diastolic and end-systolic volume indexes and left ventricular ejection fraction (LVEF) were quantified in cine images. Ischaemia was visually defined, using the 17-segment model,[12] as the presence of a segmental perfusion deficit (PD), determined as a persistent delay (in at least three consecutive temporal images, in comparison with other segments in the same slice) during the first pass of contrast through the myocardium after vasodilator infusion. The ischaemic burden was defined as the number of segments that showed post-stress PD. The presence of stress-induced PD was ruled out in segments exhibiting transmural late gadolinium enhancement (LGE) and segments with simultaneous PD and non-transmural LGE in which the extent of PD did not exceed the extent of LGE. The ischaemic burden was also analysed as a continuous variable and dichotomized as non-extensive (≤5 segments) and extensive (>5 segments with PD). This cut-off value was derived from this same series of patients based on its ability to predict all-cause death in the entire population.[11] Late gadolinium enhancement extent was visually defined as the number of segments with LGE. Inter- and intra-observer variability for all parameters used in the present registry were <5% and have been previously reported.[11]

Cardiac magnetic resonance-related revascularization

Cardiac magnetic resonance-related revascularization was defined as those procedures (either coronary artery bypass grafting or percutaneous coronary intervention) performed within 3 months following the index vasodilator stress CMR study.

Endpoint and follow-up

The clinical endpoint was new-onset HF. New-onset HF included a new HF diagnosis at the outpatient level according to current ESC guidelines or hospitalization for acute HF (AHF). AHF hospitalization was defined as any unplanned in-hospital stay with symptoms and signs of HF longer than 24 h requiring intravenous therapy. Outpatient HF diagnosis required the diagnosis label in the electronic medical record and the use of diuretics. Follow-up was centrally carried out from October 2018 to November 2018 by four cardiologists authorized by the local ethics committee using the unified electronic regional health system registry. Acute coronary syndrome (Killip >I) was not considered admission for AHF. Additionally, all-cause mortality, MI, and non-CMR-related revascularization were registered during follow-up. Follow-up was carried out centrally from October 2018 to November 2018 by four cardiologists authorized by the local ethics committee, using the unified electronic regional health system registry.

Statistical analysis

Continuous variables are presented as mean (± standard deviation) or median (interquartile range), as appropriate. Categorical variables are expressed as percentages. Baseline continuous variables were compared according to sex using the Student's *t*-test or Wilcoxon rank-sum test, as appropriate. Discrete variables were compared using the χ^2 test.

The association of sex with time-incident HF was assessed using multivariate Cox proportional hazards regression models accounting for the effect of competing events using the Fine and Gray method.[13] All-cause mortality, MI, and revascularization that occurred during follow-up were considered competing events. All covariates shown in *Table 1* were evaluated in regression models for predictive purposes. To minimize the residual confounding and indication bias, the covariates included in the multivariate models were selected based on their biological/clinical plausibility, regardless of the *P*-value. The linearity assumption for all continuous variables was simultaneously tested and transformed, if appropriate, with fractional polynomials.[14] Finally, we derived a reduced and parsimonious model by using backward step-down selection. The final model included the following 12 covariates: age, diabetes mellitus, hypertension, dyslipidaemia, smoking status, prior known CAD, prior revascularization, left bundle branch block, ability to perform an electrocardiography stress test, CMR LVEF, CMR ischaemic burden (0–17 segments), and segments with LGE. Under the same multivariate setting, subgroup analyses were performed. Two sensitivity analyses were also performed. The first included body mass index into the final multivariate model ($N = 5392$). The second included only patients with LVEF ≥50%, without ischaemia or necrosis on CMR ($N = 2826$).

The proportionality assumption for the hazard function over time was tested using the Schoenfeld residuals. The multivariate model's discriminatory ability was evaluated, with Harrell's C-statistics showing an adequate performance (0.799).

We set a two-sided *P*-value of <0.05 as the threshold for statistical significance. Stata 15.1 [STATA Statistical Software, Release 15 (2017); StataCorp LP, College Station, TX, USA] was used for the analysis.

Results

The patients' mean age was 65.1 ± 11.5 years, and 2289 (38.8%) were women. Baseline characteristics across sex are presented in *Table 1*. Overall, women were older, exhibited more frequent hypertension and dyslipidaemia, and had higher LVEF. Men had a more frequent history of smoking, CAD, and coronary revascularization. Likewise, men showed greater ischaemic burden, LGE, and underwent CMR-related angiography and revascularization more frequently (*Table 1*).

Women and risk of new-onset heart failure

During a median follow-up of 4.5 years (1.8–7.8), we registered 610 (10.3%) deaths, 191 (3.2%) MI, 905 (15.3%) revascularization

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

Table 1 Baseline characteristics relative to sex and new-onset heart failure

	Women (*N* = 2289)	Men (*N* = 3610)	*P*-value	No new-onset HF (*N* = 5585)	New-onset HF (*N* = 314)	*P*-value
Demographics and medical history						
Age (years)	68.0 ± 10.8	63.3 ± 11.6	<0.001	64.8 ± 11.5	71.2 ± 9.9	<0.001
Sex (male), *n* (%)	0	3610 (100)	<0.001	3450 (61.8)	160 (51.0)	<0.001
Sex (female), *n* (%)	2289 (100)	0	<0.001	2135 (38.2)	154 (49.0)	<0.001
Body mass index	29.1 ± 7.0	28.2 ± 4.6	<0.001	28.5 (5.7)	29.4 (4.8)	0.007
Diabetes, *n* (%)	660 (28.8)	998 (27.6)	0.323	1505 (26.9)	153 (48.7)	<0.001
Hypertension, *n* (%)	1569 (68.5)	2279 (63.1)	<0.001	3617 (64.8)	231 (73.6)	0.001
Dyslipidaemia,[a] *n* (%)	1363 (59.5)	2030 (56.2)	0.012	3204 (57.4)	189 (60.2)	0.325
Current smoker, *n* (%)	259 (11.3)	797 (22.1)	<0.001	1020 (18.3)	36 (11.5)	0.002
Family history of IHD, *n* (%)	124 (5.4)	185 (5.1)	0.623	296 (5.3)	13 (4.1)	0.369
Previous IHD, *n* (%)	589 (25.7)	1634 (45.3)	<0.001	2087 (37.4)	136 (43.3)	0.034
Previous revascularization, *n* (%)	295 (12.9)	1105 (30.6)	<0.001	1316 (23.6)	84 (26.8)	0.196
Ability to perform an electrocardiography stress test, *n* (%)	458 (20.0)	762 (21.1)	0.310	1192 (21.3)	28 (8.9)	<0.001
ECG						
ST-segment depression, *n* (%)	75 (3.3)	101 (2.8)	0.292	163 (2.9)	13 (4.1)	0.216
T-wave inversion, *n* (%)	183 (8.0)	261 (7.2)	0.278	415 (7.4)	29 (9.2)	0.238
LBBB, *n* (%)	165 (7.2)	152 (4.2)	<0.001	291 (5.2)	26 (8.3)	0.019
CMR indices						
LVEF (%)	67.4 ± 10.1	62.0 ± 10.9	<0.001	64.4 ± 10.8	59.3 ± 13.0	<0.001
LVEF <50%, *n* (%)	165 (7.2)	583 (16.1)	<0.001	657 (11.8)	91 (29.0)	<0.001
Number of PD segments	1.5 ± 2.6	2.4 ± 2.9	<0.001	2.0 ± 2.8	2.9 ± 3.3	<0.001
Any segment with PD, *n* (%)	746 (32.6)	1791 (49.6)	<0.001	2369 (42.4)	168 (53.5)	<0.001
Number of LGE segments	0.6 ± 1.6	1.5 ± 2.3	<0.001	1.1 ± 2.1	1.5 ± 2.5	0.001
Any segment with LGE, *n* (%)	436 (19.1)	1505 (41.7)	<0.001	1816 (32.5)	125 (39.8)	0.007
CMR-related revascularization						
CMR-related coronary angiography, *n* (%)	330 (14.4)	700 (19.4)	<0.001	951 (17.0)	79 (25.2)	<0.001
CMR-related revascularization, *n* (%)	153 (6.7)	386 (10.7)	<0.001	497 (8.9)	42 (13.4)	0.007

Continuous values are expressed as mean ± SD.
CMR, cardiovascular magnetic resonance; HF, heart failure; IHD, ischaemic heart disease; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; PD, perfusion deficit; SD, standard deviation.
[a]Dyslipidaemia was defined as total cholesterol ≥200 mg/dL (5.2 mmol/L) or high-density lipoprotein <40 mg/dL (1.03 mmol/L) for men or high-density lipoprotein <50 mg/dL (1.3 mmol/L) for women or triglycerides ≥150 mg/dL (1.7 mmol/L) or low-density lipoprotein (LDL) ≥130 mg/dL (3.4 mmol/L) according to the National Cholesterol Education Program Adult Treatment Panel III.[b] Patients who met one or more of these criteria were categorized as having dyslipidaemia. Those treated with a lipid-lowering agent due to a prior diagnosis of dyslipidaemia were also classified as having dyslipidaemia.
[b]National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–3421.

procedures, and 314 (5.3%) new-onset HF. Baseline characteristics according to new-onset HF status are presented in *Table 1*. In summary, those with new-onset HF presented a worse baseline risk profile, including lower mean LVEF and greater ischaemic and LGE extension (*Table 1*).

More than half of the HF diagnoses were in an AHF hospitalization setting [61.8% (*N* = 194)]. In these cases, the median (p25–p75) value of NT-proBNP on admission was 3210 pg/mL (1766–5600), and 122 (62.9%) of these patients showed LVEF >50%, being these rates higher in women (78.9% vs. 47.9%, *P* < 0.001). Except for LVEF and age, we did not find significant differences across sex in the other baseline characteristics of patients with AHF hospitalizations (Supplementary material online, *File S2*).

Women showed unadjusted higher new-onset HF rates (1.25 vs. 0.83 per 100 person-years, *P* = 0.001). In contrast, women showed lower unadjusted rates of death (1.65 vs. 2.0 per 100 person-years, *P* = 0.013), MI (0.44 vs. 0.71 per 100 person-years, *P* = 0.003), and non-CMR-related revascularizations (1.0 vs. 1.57 per 100 person-years, *P* < 0.001). Higher rates of new-onset HF persisted in women after accounting for competing events (0.93 vs. 0.64 per 100 person-years, *P* = 0.006). A cumulative incidence plot for new-onset HF, accounting for all-cause mortality, MI, and revascularization procedures as competing events, confirmed the higher incidence of new-onset HF in women during the entire follow-up (*Figure 2*). Incidence of competing events across sex are presented in Supplementary material online, *Figure S1*. Women showed a significantly higher

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

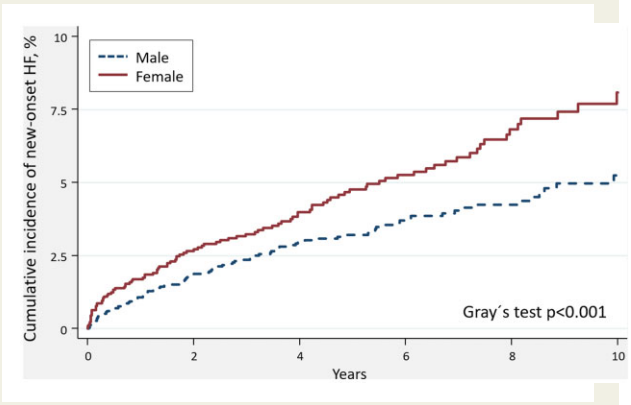


Figure 2 Cumulative incidence of new-onset heart failure. HF, heart failure.

incidence of new-onset AHF hospitalizations ($P = 0.025$) and a statistical trend to higher incidence when the endpoint was an ambulatory HF diagnosis ($P = 0.081$), as is shown in Supplementary material online, *Figure S2*. After multivariate adjustment, female sex carried an increased risk of new-onset HF [hazard ratio (HR) 1.61, 95% confidence interval (CI) 1.21–2.13; $P = 0.001$]. Under the same multivariate adjustment, we found that the association of female sex with higher risk was highly significant when the endpoint was new-onset AHF hospitalizations (HR 1.58, 95% CI 1.09–2.28; $P = 0.015$) and borderline significant for ambulatory HF diagnosis (HR 1.57, 95% CI 0.98–2.51; $P = 0.060$). Estimates of risks of all the covariates included in the final multivariate model are shown in Supplementary material online, *File S3*.

In women, the excess risk of new-onset HF did not significantly differ across the most relevant demographic and cardiovascular (CV) risk factor subgroups and CMR-related parameters, as shown in *Figure 3*. A sensitivity analysis, which forced into the multivariate model the same prior 12 covariates included in the full model plus body mass index ($N = 5392$) continued to display an excess of risk for women (HR 1.53, 95% CI 1.13–2.06; $P = 0.006$). Likewise, we did not find a differential effect of sex across obesity status (*Figure 3*).

Impact of left ventricular ejection fraction on heart failure sex-related risk

We found an adjusted significant differential effect across sex along the continuum of LVEF (P-value for interaction = 0.007). At lower LVEF, there was a higher risk in both sexes (*Figure 4A and B*). However, and compared with men, new-onset HF's risk was higher in women at LVEF >55% and upward (*Figure 4C*).

Impact of ischaemic and necrosis extension on heart failure sex-related risk

Ischaemic and necrosis extension as the main terms were not associated with new-onset HF risk (Supplementary material online, *Figure S3*). Likewise, we did not find a differential association between sex and risk of new-onset HF along the continuum of ischaemic (P-value for interaction = 0.508) and necrosis burden (P-value for interaction = 0.425), as shown in *Figure 5*.

Sex and risk of new-onset heart failure in those with preserved ejection fraction and absence of ischaemia and necrosis on baseline cardiac magnetic resonance

In this sensitivity analysis that included 2826 patients with LVEF ≥50% and without CMR ischaemia and necrosis, women had a higher incidence of new-onset HF (Supplementary material online, *Figure S4*). Under the same multivariate setting (excluding LVEF, CMR ischaemia, and necrosis), women remained to display a higher risk of new-onset HF (HR 2.22, 95% CI 1.23–3.99; $P = 0.008$).

Discussion

In a real-life consecutive and prospective registry that included known or suspected CAD subjects and free from HF, and adjusting for crucial competing events, we identified a significantly increased risk of new-onset HF in women (Graphical abstract). We also found a sex-related difference regarding the influence of baseline LVEF on the risk of new-onset HF. In both sexes, lower LVEF was associated with higher risk; however, and compared with men, women displayed a higher risk in certain ranges of preserved LVEF. Specifically, at LVEF >55%, women were at higher risk. Interestingly, we could not find an influence of ischaemic and necrosis detected by CMR in HF sex-related differences.

Incident heart failure and sex in patients with coronary artery disease: an under-examined endpoint

Prior studies have highlighted differences in symptoms, care received, and clinical outcomes between men and women with acute MI.[15–17] A recent systematic review, including 39 studies, reported that age, comorbidities, and treatment differences explained most of the mortality risk excess found in women.[18] However, little is known about the differences between women and men regarding HF risk in patients with ambulatory known or suspected CAD. Following MI, a recent study of 45 064 patients with a first MI found that women remain at a higher risk than men of developing HF within 5 years following ST-elevation myocardial infarction (STEMI) or non-STEMI, even after accounting for traditional confounders, including coronary anatomy.[8] In contrast to acute coronary syndromes, in subjects without a history of CAD, some data suggest survival and prognostic advantage in women vs. men.[19] This is the first study reporting an excess HF risk in women in a large contemporary cohort of known or suspected CAD. The excess HF risk found in women was consistent in the current study despite thorough adjustment, including age, traditional CV risk factors, revascularization procedures, LVEF, ischaemic burden, and accounting for competing events during follow-up.

Furthermore, the results were homogeneous in the most important subgroups. Several factors minimize the possibility that most of these sex-related differences may be explained by different access to a diagnostic test, revascularization rates, calendar year, LVEF, and severity of ischaemic burden. First, all these subjects underwent a CMR

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

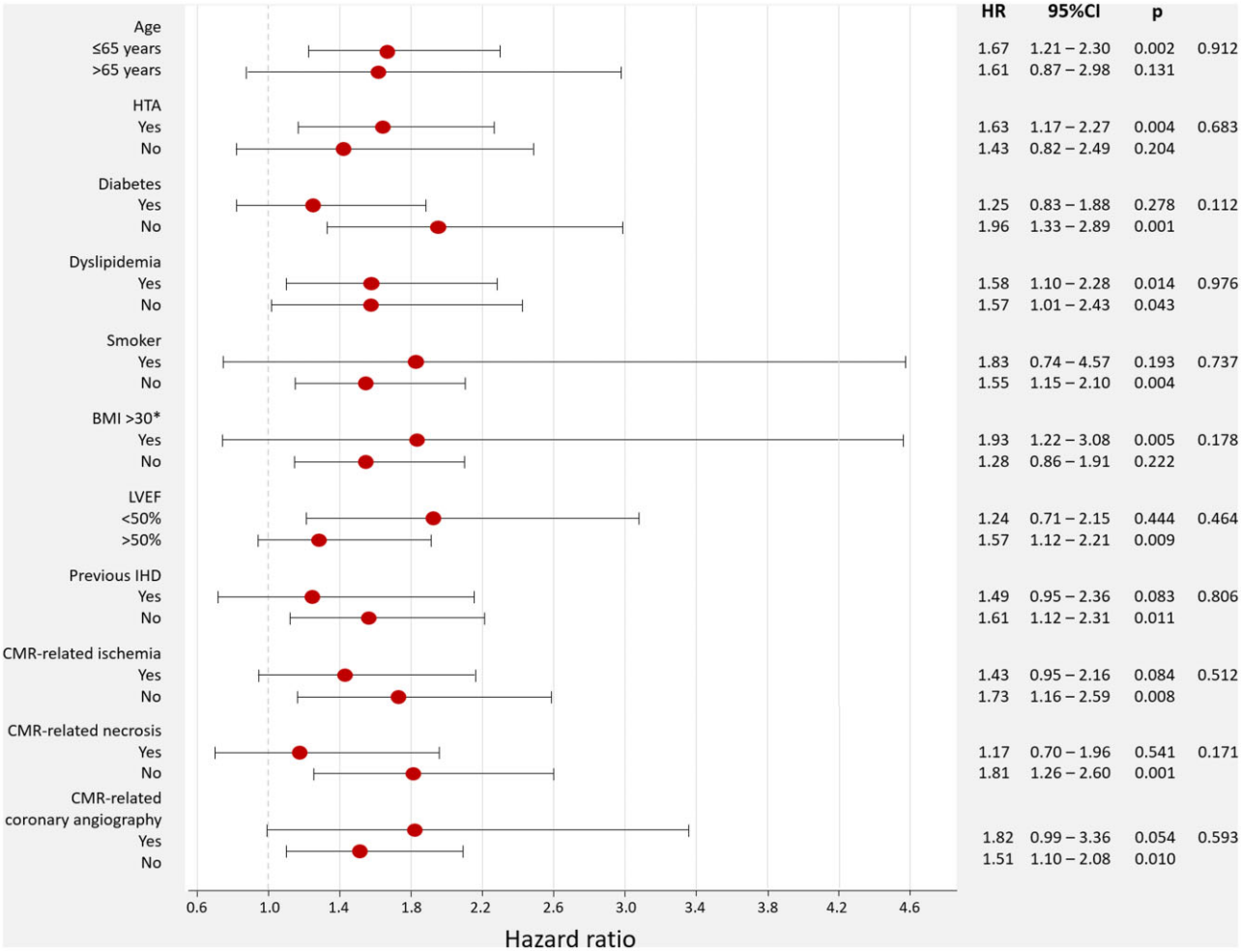


Figure 3 Risk of new-onset heart failure in women across the most relevant subgroups. BMI, body mass index; CI, confidence interval; CMR: cardiovascular magnetic resonance; HR, hazard ratio; HTA: hypertension; IHD, ischaemic heart disease; LVEF: left ventricular ejection fraction. *Analysis in 5392 subjects.

with a morphological, functional, and ischaemic assessment. Second, despite revascularization having failed to show a prognostic benefit over optimal medical treatment in chronic coronary syndromes in recent randomized clinical trials and meta-analysis,[20,21] estimates of risk were adjusted for revascularization procedures. Likewise, the multivariate analysis included the most critical confounders and accounted for events that may substantially modify HF risk during follow-up. Finally, treatment of chronic coronary syndromes has not substantially changed in recent years;[1] thus, we believe these findings may be extrapolated to current clinical practice.

Women and risk of heart failure in coronary artery disease: a pathobiological explanation

Non-coronary acute chest pain, non-obstructive CAD, non-atherosclerotic disease, and lesser ischaemic burden, but greater angina are more frequent in women than in men.[6,22,23] Indeed, almost two-thirds of women with persistent symptoms and clinical signs of ischaemia have no significant obstructive CAD (INOCA) on angiography, vs. only one-third of men.[6,22] However, this latter scenario does not confer a good prognosis.[6,22] In line with the present findings, prior authors have reported that in women with INOCA, the most frequent adverse cardiac event is HF hospitalization.[6,22] Thus, we postulate that coronary microvascular dysfunction might be a crucial pathophysiological link explaining the excess risk in women with CAD, INOCA, and HF. Also, other cardiac and non-cardiac differences could underlie these differences. For instance, women tend to have lower left ventricle volumes and mass, greater left ventricle contractility, small coronary vessels, and faster heart rate.[24] Additionally, hypertension, diabetes, obesity, and inactivity are other predominant risk factors in women.[24]

Finally, we cannot exclude the possibility of misclassification in the diagnosis workout. It is well known that symptoms and signs of HF offer a limited accuracy for diagnosis.[25] It is also well reported that women display a more atypical clinical HF presentation.[26,27] Probably,

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

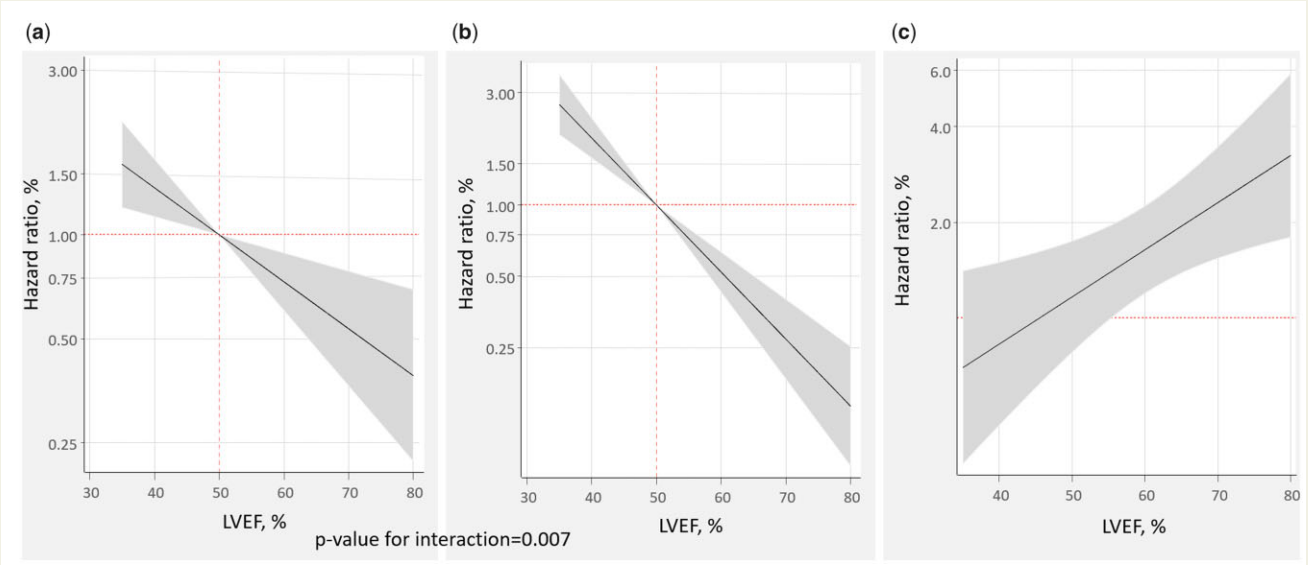


Figure 4 Adjusted risk of new-onset heart failure on the left ventricular ejection fraction continuum. (*A*) Women. (*B*) Men. (*C*) Women vs. men. LVEF, left ventricle ejection fraction.

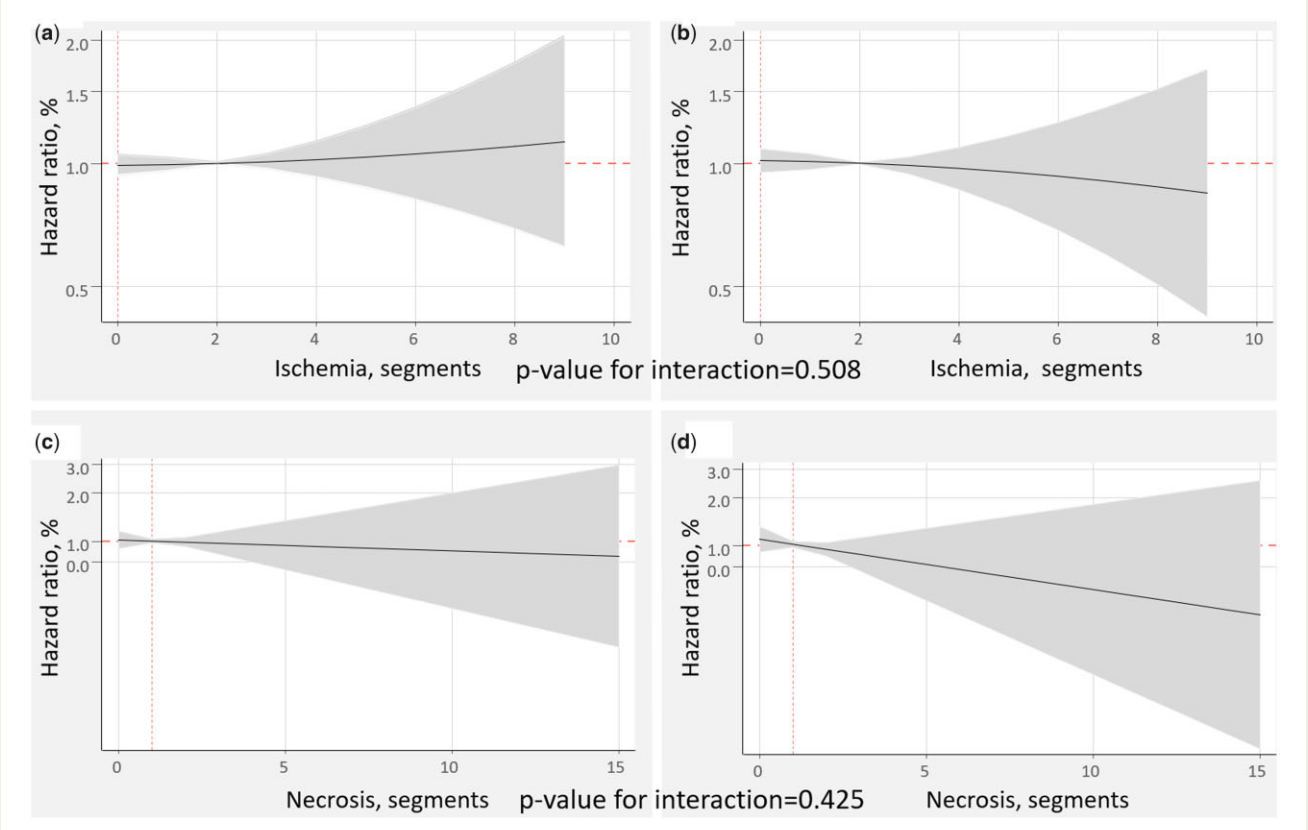


Figure 5 Adjusted risk of new-onset heart failure according to cardiac magnetic resonance-derived ischaemia and necrosis. (*A*) Women, ischaemic burden. (*B*) Men, ischaemic burden. (*C*) Women, necrosis burden. (*D*) Men, necrosis burden.

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

some of the women were misinterpreted already showing HF at the presentation.

Clinical implications

We envision potential clinical implications for diagnosis, risk stratification, and monitoring derived from these findings. First, it may be that in certain circumstances, the clinical presentation in women with known or suspected CAD may represent non-typical clinical presentations of already existing symptomatic HF (atypical presentation of HF in women). Thus, clinicians should consider and accurately diagnose coronary microvascular dysfunction and rule out a clinically symptomatic HF in INOCA patients. Second, given the non-negligible risk of new-onset HF in this study, further studies should incorporate HF endpoints in the risk stratification workup of patients with known or suspected CAD. Third, according to the current findings, women are at higher risk of HF regardless of the ischaemic burden. Thus, conversely to what we find in daily clinical practice in which negative or low ischaemic burden leads to reduced awareness, we foresee women as one of the subgroups in which a differential diagnostic workup and close monitoring for early identification of HF might be justified. Additionally, this subset of women may also require a specific approach for risk stratification and treatment.[28,29]

Limitations

Some limitations should be outlined. First, several unmeasured confounders might play a meaningful role. We do not have granular information on patients' symptoms, coronary anatomy, or medical treatment. Second, we excluded patients with a prior clinical diagnosis of HF; however, we cannot rule out undiagnosed HF in some patients. Third, the lack of assessment of body mass index in all the patients and the non-availability of anthropometric measures and body composition analysis preclude the evaluation of these variables' influence on HF risk in both sexes. Fourth, we did not register important HF parameters (imaging, natriuretic peptides, and therapeutics) of those patients ascertained as new-onset HF, especially in those with ambulatory diagnosis. Finally, specific assessment of coronary anatomy, coronary flow reserve, or regional patterns of ischaemia suggesting microvascular dysfunction would have been valuable in unravelling these patients' pathobiology.

Conclusions

Women with known or suspected CAD are at higher risk of new-onset HF. Further studies should be performed to confirm the current findings and disentangle the pathophysiological mechanism behind these findings.

Clinical perspectives

Competencies in medical knowledge

Little is known about sex and new-onset HF in patients with known or suspected CAD. Compared with men, women with CAD more often developed new-onset HF, mainly with preserved LVEF.

Translational outlook

Our data suggest that irrespective of LVEF, women with known or suspected CAD should be closely monitored for early identification and management of new-onset HF.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Funding

This work was supported by the Instituto de Salud Carlos III and co-funded by Fondo Europeo de Desarrollo Regional (FEDER) [PI17/01836, PI20/00637, CIBERCV 16/11/00486, 16/11/00420, and 16/11/00403].

Conflict of interest: none declared.

References

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Áinle FN, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J* 2019;**54**:1901647.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
3. Young L, Cho L. Unique cardiovascular risk factors in women. *Heart* 2019;**105**:1656–1660.
4. Manfrini O, Yoon J, van der Schaar M, Kedev S, Vavlukis M, Stankovic G, Scarpone M, Milicic D, Vasiljevic Z, Badimon L, Cenko E, Bugiardini R. Sex differences in modifiable risk factors and severity of coronary artery disease. *J Am Heart Assoc* 2020;**9**:e017235.
5. Pagidipati NJ, Mudrick DW, Chiswell K, Brucker A, Peterson ED, Douglas PS. Sex differences in long-term outcomes of patients across the spectrum of coronary artery disease. *Am Heart J* 2018;**206**:51–60.
6. Wei J, Cheng S, Merz CNB. Coronary microvascular dysfunction causing cardiac ischemia in women. *JAMA* 2019;**322**:2334.
7. Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009;**53**:13–20.
8. Ezekowitz JA, Savu A, Welsh RC, McAlister FA, Goodman SG, Kaul P. Is there a sex gap in surviving an acute coronary syndrome or subsequent development of heart failure? *Circulation* 2020;**142**:2231–2239.
9. Bodi V, Sanchis J, Lopez-Lereu MP, Nunez J, Mainar L, Monmeneu JV, Husser O, Dominguez E, Chorro FJ, Llacer A. Prognostic value of dipyridamole stress cardiovascular magnetic resonance imaging in patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1174–1179.
10. Bodi V, Husser O, Sanchis J, Núñez J, Monmeneu JV, López-Lereu MP, Bosch MJ, Rumiz E, Miñana G, García C, Diago JL, Chaustre F, Moratal D, Gómez C, Aguilar J, Chorro FJ, Llacer Á. Prognostic implications of dipyridamole cardiac MR imaging: a prospective multicenter registry. *Radiology* 2012;**262**:91–100.
11. Marcos-Garces V, Gavara J, Monmeneu JV, Lopez-Lereu MP, Bosch MJ, Merlos P, Perez N, Rios-Navarro C, De Dios E, Bonanad C, Racugno P, Bellver Navarro A, Ventura Perez B, Aguilar Botella J, Ventura S, Mainar L, Canoves J, Pellicer M, Moratal D, Miñana G, Nuñez J, Chorro FJ, Bodi V. Vasodilator stress CMR and

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024

all-cause mortality in stable ischemic heart disease: a large retrospective registry. *JACC Cardiovasc Imaging* 2020;**13**:1674–1686.
12. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;**105**:539–542.
13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509.
14. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer; 2001.
15. Chou AF, Wong L, Weisman CS, Chan S, Bierman AS, Correa-de-Araujo R, Scholle SH. Gender disparities in cardiovascular disease care among commercial and Medicare managed care plans. *Womens Health Issues* 2007;**17**:139–149.
16. Chang W-C, Kaul P, Westerhout CM, Graham MM, Fu Y, Chowdhury T, Armstrong PW. impact of sex on long-term mortality from acute myocardial infarction vs. unstable angina. *Arch Intern Med* 2003;**163**:2476–2484.
17. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX, Boden WE, Roe MT, Ohman EM, Gibler WB, Newby LK. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;**45**:832–837.
18. Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction: a systematic review. *Circulation* 2014;**130**:757–767.
19. Peters SAE, Colantonio LD, Chen L, Bittner V, Farkouh ME, Rosenson RS, Jackson EA, Dluzniewski P, Poudel B, Muntner P, Woodward M. Sex differences in incident and recurrent coronary events and all-cause mortality. *J Am Coll Cardiol* 2020;**76**:1751–1760.
20. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE, Rockhold FW, Broderick S, Ferguson TB, Williams DO, Harrington RA, Stone GW, Rosenberg Y; ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;**382**:1395–1407.
21. Bangalore S, Maron DJ, Stone GW, Hochman JS. Routine revascularization versus initial medical therapy for stable ischemic heart disease: a systematic review and meta-analysis of randomized trials. *Circulation* 2020;**142**:841–857.
22. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL, Camici PG, Chilian WM, Clayton JA, Cooper LS, Crea F, Di Carli M, Douglas PS, Galis ZS, Gurbel P, Handberg EM, Hasan A, Hill JA, Hochman JS, Iturriaga E, Kirby R, Levine GN, Libby P, Lima J, Mehta P, Desvigne-Nickens P, Olive M, Pearson GD, Quyyumi AA, Reynolds H, Robinson B, Sopko G, Taqueti V, Wei J, Wenger N. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation* 2017;**135**:1075–1092.
23. Reynolds HR, Shaw LJ, Min JK, Spertus JA, Chaitman BR, Berman DS, Picard MH, Kwong RY, Bairey-Merz CN, Cyr DD, Lopes RD, Lopez-Sendon JL, Held C, Szwed H, Senior R, Gosselin G, Nair RG, Elghamaz A, Bockeria O, Chen J, Chernyavskiy AM, Bhargava B, Newman JD, Hinic SB, Jaroch J, Hoye A, Berger J, Boden WE, O'Brien SM, Maron DJ, Hochman JS; for the ISCHEMIA Research Group. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol* 2020;**5**:773–786.
24. Bozkurt B, Khalaf S. Heart failure in women. *Methodist Debakey Cardiovasc J* 2017;**13**:216–223.
25. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJV, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.
26. Eisenberg E, Di Palo KE, Piña IL. Sex differences in heart failure. *Clin Cardiol* 2018;**41**:211–216.
27. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J* 2019;**40**:3859–3868c.
28. Sciomer S, Moscucci F, Salvioni E, Marchese G, Bussotti M, Corrà U, Piepoli MF. Role of gender, age and BMI in prognosis of heart failure. *Eur J Prev Cardiol* 2020;**27**:46–51.
29. Veenis JF, Rocca HB, Linssen GC; CHECK-HF Investigators. Impact of sex-specific target dose in chronic heart failure patients with reduced ejection fraction. *Eur J Prev Cardiol* 2020; doi:10.1177/2047487320923185.

Erratum

doi:10.1093/eurjpc/zwab071
Online publish-ahead-of-print 20 June 2021

Erratum to: EAPC Core Curriculum for Preventive Cardiology

Eur J Prev Cardiol 2021; https://doi:10.1093/eurjpc/zwab017.

The originally published version of this article contained an error in the title. We have since corrected this to remove the text '(compare to ESC Core Curriculum for the Cardiologist).' OUP apologizes for this error.

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/eurjpc/article/28/15/1711/6273046 by guest on 18 April 2024