

Cardiac magnetic resonance for prophylactic implantable-cardioverter defibrillator therapy international study: prognostic value of cardiac magnetic resonance-derived right ventricular parameters substudy

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Aims

Right ventricular systolic dysfunction (RVSD) is an important determinant of outcomes in heart failure (HF) cohorts. While the quantitative assessment of RV function is challenging using 2D-echocardiography, cardiac magnetic resonance (CMR) is the gold standard with its high spatial resolution and precise anatomical definition. We sought to investigate the prognostic value of CMR-derived RV systolic function in a large cohort of HF with reduced ejection fraction (HFrEF).

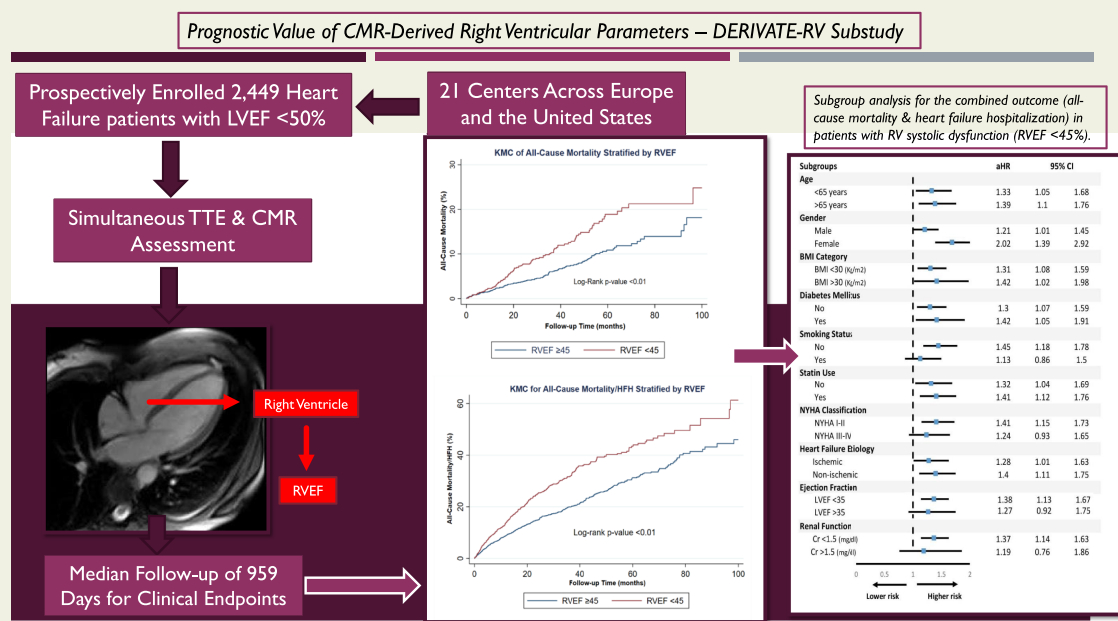
Methods and results

Study cohort comprised of patients enrolled in the CarDiac MagnEtic Resonance for Primary Prevention Implantable CardioVerter DefibrillAtor ThERapy registry who had HFrEF and had simultaneous baseline CMR and echocardiography ($n = 2449$). RVSD was defined as RV ejection fraction (RVEF) $<45\%$. Kaplan–Meier curves and cox regression were used to investigate the association between RVSD and all-cause mortality (ACM). Mean age was 59.8 ± 14.0 years, 42.0% were female, and mean left ventricular ejection fraction (LVEF) was 34.0 ± 10.8 . Median follow-up was 959 days (interquartile range: 560–1590). RVSD was present in 936 (38.2%) and was an independent predictor of ACM (adjusted hazard ratio = 1.44; 95% CI [1.09–1.91]; $P = 0.01$). On subgroup analyses, the prognostic value of RVSD was more pronounced in NYHA I/II than in NYHA III/IV, in LVEF $<35\%$ than in LVEF $\geq 35\%$, and in patients with renal dysfunction when compared to those with normal renal function.

Conclusion

RV systolic dysfunction is an independent predictor of ACM in HFrEF, with a more pronounced prognostic value in select subgroups, likely reflecting the importance of RVSD in the early stages of HF progression.

Graphical Abstract



Keywords

heart failure • right ventricular dysfunction • cardiac magnetic resonance • heart failure hospitalization • ejection fraction

Introduction

Heart failure (HF) is a heterogeneous disorder with a wide range of cardiomyopathies, which often cross the arbitrary left ventricular (LV) ejection fraction (EF) boundaries.¹ The variable longitudinal trajectory of HF, coupled with the limited prognostic value of demographic and clinical data, necessitates the exploratory search for noninvasive imaging markers for better prognostication of incident

adverse events, and for guidance of medical, percutaneous, and surgical therapies.

Right ventricular (RV) dysfunction has been recognized as an important determinant of clinical outcomes in HF cohorts.^{2–4} However, quantitative assessment of RV function is challenging in a routine clinical setting, as the geometrical complexity of the RV limits the ability of direct volumetric assessment by traditional two dimensional (2D) echocardiography. Other modalities have also been used for the evaluation of RV function, such as radionuclide

ventriculography,² right heart catheterization,⁵ and 3D echocardiography.⁶ Cardiac magnetic resonance (CMR), however, is the 'gold standard' for volumetric cardiac assessment and quantification due to its high level of spatial resolution, precise definition of anatomy, and excellent reproducibility.⁷ Few studies have investigated the prognostic value of CMR-derived RV volumetric parameters in HF with reduced EF (HFrEF).^{2,8–12} To this date, the significance of quantitative measures of RV dysfunction is not fully elucidated, primarily due to the small sample sizes and limited scope of the published data. Further, the incremental prognostic value of quantitative RV parameters of structure and function, on top of clinical parameters, is not known especially across various subgroups of HFrEF.

In this retrospective analysis, we utilized a large, multicentre, prospective cohort of HFrEF from the DERIVATE 'CarDiac MagnEtic Resonance for Primary Prevention Implantable CardioVerter DefibrillAtor ThErapy' registry.¹³ The primary objective was to explore the correlation between CMR-derived quantitative parameters of RV systolic function, mainly the RVEF, in predicting all-cause mortality (ACM) and HF hospitalizations (HFHs) amongst various subgroups of HFrEF patients.

Methods

DERIVATE registry

The design and rationale of the DERIVATE registry along with the protocols, inclusion and exclusion criteria are described in details in a previous publication.¹³ In brief, DERIVATE is an international, multicentre, prospective, observational study that enrolled consecutive HFrEF patients at 21 sites across Europe and the United States. Included patients underwent baseline evaluation with both transthoracic echocardiography (TTE) and CMR imaging.¹³ Inclusion criteria included the following: (i) age ≥ 18 years old, (ii) chronic HF with >3 months since the last decompensation, (iii) LVEF $<50\%$ at initial TTE evaluation, and (iv) both TTE and CMR are performed within 3 months of each other. Exclusion criteria included the following: (i) decompensated HF within 3 months of enrollment, (ii) recent myocardial infarction (<40 days), (iii) unstable angina, (iv) severe valvular disease, (v) hypertrophic cardiomyopathy, (vi) Takotsubo cardiomyopathy, (vii) cardiac amyloidosis, and (viii) congenital heart disease. The institutional ethical committees of the participating centres approved the protocol, and all patients gave written informed consent.

Study design

The target population of DERIVATE was patients with clinical history of chronic HFrEF. Chronic HF was defined as >3 months from the last decompensated HF presentation according to the ACC/AHA classification.¹⁴ The ACC/AHA definition of HF with preserved LVEF had been established using a reference of LVEF $\geq 50\%$, and hence, this study included patients with HF and EF $<50\%$ (i.e. HFrEF). Severe LV dysfunction was defined as LVEF $<35\%$ according to the initial TTE evaluation. RV systolic dysfunction (RVSD) was defined as RVEF $<45\%$ by CMR based on cut-off used in previous publications.^{8,10,12,15} Image acquisition protocols for both TTE and CMR can also be found in previous publications.^{13,16}

Objectives and endpoints

The primary objective of the DERIVATE registry was to identify, quantify, and integrate CMR parameters with demographic, clinical, and TTE data for risk stratification in patients with HFrEF. The goal of present analysis was to investigate the correlation between CMR-derived quantitative parameters of RV systolic function, the RVEF, and clinical endpoints. ACM was the primary endpoint of the present analysis. The secondary endpoint was a composite outcome consisting of ACM and HFHs.

Follow-up

Patient follow-up was performed at each local institution by dedicated personnel. The minimum follow-up period was 12 months. Quality control and study monitoring was performed in accordance with ICH-E6 Good Clinical Practice guidelines and applicable local regulations.

Statistical analysis

The rationale for sample size determination of the DERIVATE registry was detailed in a prior publication.¹³ All statistical analyses were performed with the use of STATA 16 (State Corp LLC, College Station, Texas). A p value <0.05 was considered statistically significant. Baseline characteristics of patients were stratified according to RVSD (RVEF $\geq 45\%$ vs. RVEF $<45\%$). Descriptive statistics were used to characterize both groups. Student's independent t -test, Chi-square, or Fischer's exact test were used as appropriate to compare the distribution of continuous and categorical variables, respectively. Stratified according to RVSD, survival curves related to primary endpoints were plotted using the Kaplan–Meier (KM) method with right-censoring at 100 months due to a significant proportion of missing observations after that time period (57 of the 2449 study subjects had follow-up past 100 months). The log-rank test was used to assess for equality of survival functions.

Univariate Cox proportional hazard models were used to identify the variables associated with ACM. Significant variables (P value <0.05) at the univariate analyses were included in the final multivariable Cox proportional hazard models, in a stepwise fashion. The proportional-hazards assumption for Cox models was investigated based on Schoenfeld residual method as well as graphically. Results of the Cox proportional hazard models are reported as hazard ratios (HRs), and their correspondent 95% confidence intervals (CIs). Using the same covariates of the Cox models, subgroup analyses were conducted for study endpoints in patients with RVSD, and adjusted HHRs (aHRs) for various subgroups are summarized in forest plots.

Missing data for covariates were handled with the use of multiple imputation. Multiple imputation models incorporated all available baseline data. However, covariates with significant percentage ($>20\%$) of missing data [i.e. tricuspid annular plane systolic excursion (TAPSE), pulmonary arterial systolic pressure (PASP), and pro-hormone B-type natriuretic peptide (Pro-BNP)] were not imputed or included in the Cox models. Rather, they were explored via KM curve subgrouping ([Supplementary data online](#)). The 10-fold cross validation method was used to assess the performance of the Cox proportional hazards regression model. The area under receiver operator curve (AUROC) was used as a performance measure of the model predictions and reported as the mean and standard deviation (SD) of the AUROC values.

Results

A total of 2449 subjects with HFrEF were included in the analysis. Mean age was 59.8 ± 14.0 years and 42.0% were female. RVSD

Table 1 Baseline characteristics of the study cohort stratified by RVSD (defined as RVEF <45%)

	No RVSD (N = 1513)	RVSD (N = 936)	Total Cohort (N = 2449)	P-value
General characteristics				
Age (mean ± SD, years)	59.4 ± 13.9	60.5 ± 14.0	59.8 ± 14.0	0.07
Age > 65 years, n (%)	622 (41.1)	407 (43.5)	1029 (42.0)	0.09
Female; n (%)	418 (27.6)	168 (17.9)	586 (23.9)	<0.01
BMI (mean ± SD, Kg/m ²)	26.4 ± 4.5	26.8 ± 4.9	26.5 ± 4.6	0.07
BSA (mean ± SD, m ²)	1.88 ± 0.27	1.91 ± 0.24	1.89 ± 0.27	0.01
Family history of CAD; n (%)	448/1472 (30.4)	266/823 (32.3)	714/2295 (31.1)	0.55
Smoker; n (%)	556 (36.8)	409 (43.7)	965 (39.4)	<0.01
Hypertension; n (%)	763 (50.4)	464 (49.6)	1227 (50.1)	0.68
Hyperlipidemia; n (%)	649/1482 (43.8)	348/824 (42.2)	997/2306 (43.2)	0.24
Diabetes Mellitus; n (%)	285 (18.8)	245 (26.2)	530 (21.6)	<0.01
Creatinine (mean ± SD, mg/dL)	1.02 ± 0.34	1.12 ± 0.43	1.1 ± 0.4	<0.01
Left bundle branch block	371 (24.5)	242 (25.9)	613 (25.0)	0.44
Symptom burden (NYHA class)				
NYHA class I/II; n (%)	1246 (82.4)	654 (69.8)	1900 (77.6)	<0.01
NYHA class III/IV; n (%)	267 (17.6)	282 (30.1)	549 (22.4)	<0.01
Aetiology of HF				
ICM; n (%)	465 (30.7)	475 (50.8)	940 (38.4)	<0.01
Idiopathic/dilated CM; n (%)	1028 (69.3)	461 (49.2)	1509 (61.6)	<0.01
Medications				
Diuretics; n (%)	1028 (68.0)	681 (72.7)	1709 (69.7)	0.02
Statin; n (%)	684 (45.2)	504 (53.8)	1188 (48.5)	<0.01
Anti-platelet; n (%)	811 (53.6)	502 (53.6)	1313 (53.6)	0.99
Anti-coagulation; n (%)	310 (20.5)	213 (22.8)	523 (21.4)	0.20
ACE-I/ARB; n (%)	1230 (81.3)	854 (91.2)	2084 (85.1)	<0.01
Beta blocker; n (%)	1250 (82.6)	834 (89.1)	2084 (85.1)	<0.01
Any antiarrhythmic agent; n (%)	315 (20.8)	115 (12.2)	430 (17.6)	<0.01

was present in 936 (38.2%) of the cohort. Mean LVEF was 34.0 ± 10.8 percent, 22.4% had a New York Heart Association (NYHA) class of III/IV, and 38.4% had ischaemic cardiomyopathy (ICM) as the underlying aetiology for the HF. Baseline characteristics are listed in Table 1. TTE and CMR studies were acquired in all patients with a median interval of 3 days [interquartile range (IQR): 2–5 days] between TTE and CMR. The median follow-up time for clinical endpoints was 959 days (IQR: 560–1590). TTE and CMR parameters of the study cohort, stratified by RVSD status, are summarized in Table 2.

Association between RVEF and clinical endpoints

At 100 months of follow-up, ACM occurred in 212 (8.7%) patients, of which 104 patients had RVSD and 108 patients had normal RVEF (non-RVSD). Mortality rate was significantly higher in patients with RVSD (104/936; 11.1%) compared to non-RVSD patients (108/1513, 7.1%); $P < 0.01$. This is also shown in KM curves (Figure 1A). RVSD was associated with higher ACM with aHR of 1.44 (95% CI: 1.09–1.91; $P = 0.01$) in the multivariable analysis (Table 3). Advanced age (>65 years), diabetes mellitus, smoking status, renal impairment (creatinine

>1.5 mg/dL), NYHA class III/IV, and ICM were independently associated with significantly higher ACM (Table 3). Results of subgroup analysis for the primary outcome of ACM are shown in Figure 2.

The composite outcome of ACM and/or HFH occurred in 645 (35.8%) patients at 100 months of follow up and was more prevalent in patients with RVSD compared to non-RVSD (31.9% vs. 22.9%, P value <0.01). KM curves are shown in Figure 1B. RVSD was associated higher ACM and/or HFH, with an aHR of 1.40 (95% CI: 1.19–1.64; $P < 0.01$) in the multivariable analysis (Table 3). Advanced age (>65 years), higher body mass index (BMI ≥ 30), diabetes mellitus, smoking status, renal impairment, and NYHA class III/IV were independent predictors of the composite outcome (Table 3). Results of subgroup analysis for the composite outcome are shown in Figure 3.

Results from 10-fold cross-validation analysis are shown in supplementary figures (see Supplementary data online, Figure S5 a and b). The mean cross-validation AUROC for the ACM model was 0.67 (95% CI: 0.61–0.70), with a SD of 0.08. The mean cross validations AUROC for the composite outcome model was 0.64 (95% CI: 0.61–0.66), with a SD of 0.04.

Table 2 TTE and cardiac MRI (CMR) parameters of the 2449 patients with HF stratified by RVSD (RVEF <45% vs. RVEF ≥45%)

	No RVSD (N = 1513)	RVSD (N = 936)	Total Cohort (N = 2449)	P-value
TTE parameters				
LVEF (mean ± SD, %)	36.5 ± 10.1	30.0 ± 10.6	34.0 ± 10.8	<0.01
LVEDV/BSA (mean ± SD, mL/m ²)	94.7 ± 34.1	104.4 ± 38.5	98.1 ± 36.0	<0.01
LVESV/BSA (mean ± SD, mL/m ²)	61.2 ± 27.8	74.7 ± 33.3	66.0 ± 30.6	<0.01
TAPSE (mean ± SD, mm)	20.8 ± 4.2	17.8 ± 4.8	19.8 ± 4.7	<0.01
PASP (mean ± SD, mmHg)	32.3 ± 10.5	39.1 ± 13.7	34.9 ± 12.3	<0.01
Diastolic dysfunction; n (%)	256/1199 (21.4)	210/571 (36.8)	466/1770 (26.3)	<0.01
CMR parameters				
CMR-LVEF (mean, %)	35.5 ± 10.1	25.3 ± 9.9	31.6 ± 11.2	<0.01
CMR-LVEDV/BSA (mL/m ²)	123.4 ± 37.7	136.3 ± 46.7	128.3 ± 41.8	<0.01
CMR-LVESV/BSA (mL/m ²)	81.4 ± 34.1	103.8 ± 43.1	90.0 ± 39.3	<0.01
CMR-LVSV (mean, mL)	79.3 ± 26.5	62.2 ± 24.1	72.8 ± 26.9	<0.01
CMR-LV mass/BSA (g/m ²)	78.9 ± 25.9	80.2 ± 28.6	79.4 ± 26.9	0.29
CMR-RVEDV/BSA (mL/m ²)	69.2 ± 20.6	86.2 ± 39.2	75.0 ± 29.4	<0.01
CMR-RVESV/BSA (mL/m ²)	29.7 ± 11.7	56.9 ± 29.7	40.1 ± 24.4	<0.01
CMR-RVEF (mean, %)	57.9 ± 7.8	33.2 ± 8.9	48.4 ± 14.5	<0.01
CMR-RVSV (mean, mL)	74.9 ± 23.5	53.0 ± 24.9	66.5 ± 26.3	<0.01

Subgroup analysis for the association between RVEF and clinical endpoints

Effect of LVEF on outcomes stratified by RV systolic function

Supplementary data online, Figure S1 depicts the linear correlation between RVEF and LVEF ($r = 0.29$, $P < 0.01$). Severe LV systolic dysfunction (LVSD) was independently associated with increased risk of ACM and/or HFH (HR = 1.53, 95% CI: 1.29–1.81, $P < 0.01$). In subgroup analysis based on LVSD severity, RVSD was found to be independently predictive of ACM (HR = 1.58, 95% CI: 1.12–2.24, $P < 0.01$) and the composite outcome of ACM and/or HFH (HR = 1.38, 95% CI 1.13–1.67, $P < 0.01$) only in the severe LVSD group (LVEF <35%). However, it did not reach statistical significance for ACM or the composite outcome in patients with LVEF ≥35%, Figures 2 and 3. KM curves for ACM in RVSD groups stratified by LVEF are shown in supplementary Figure S3 (see Supplementary data online, Figure S3g).

Effect of HF aetiology on outcomes stratified by RV systolic function

In the present cohort, non-ICM (NICM) was present in 61.6% of patients (Table 1). Compared to NICM group, ICM was independently associated with an increased risk of ACM with an aHR of 1.40 (95% CI: 1.20–1.64, $P < 0.02$) in the multivariable model (Table 3). In subgroup analysis based on HF aetiology, RVSD was predictive of ACM in patients with NICM (aHR = 1.92, 95% CI: 1.26–2.92, $P < 0.01$), but not in patients with ICM (aHR = 1.16, 95% CI: 0.78–0.71, $P = 0.46$), Figure 2. For the secondary outcome, RVSD was predictive of ACM and/or HFH in both ICM and NICM subgroups (Figure 3). KM curves for ACM in RVSD groups stratified by HF aetiology are shown in supplementary Figure S3 (see Supplementary data online, Figure S3b).

Effect of NYHA class on outcomes stratified by RV systolic function

Advanced NYHA class (III/IV) was more prevalent in patients with RVSD compared to those with normal RV systolic function (30.1% vs. 17.6%) (Table 1). Advanced NYHA class (III/IV) was independently associated with increased risk of ACM (aHR = 2.10, 95% CI: 1.58–2.79, $P < 0.01$) and the composite outcome of ACM and/or HFH (aHR = 1.81, 95% CI: 1.53–2.15, $P < 0.01$) (Table 3). Upon subgroup analysis based on NYHA class, RVSD was predictive of ACM irrespective of NYHA class category (Figure 2). However, for the composite outcome, RVSD was associated with worse outcomes in NYHA I/II group (aHR = 1.41, 95% CI: 1.15–1.73, $P < 0.01$), but not in NYHA III/IV group (aHR = 1.24, 95% CI: 0.93–1.65, $P = 0.15$), Figure 3. KM curves for ACM in RVSD groups stratified by NYHA class are shown in supplementary Figure S3 (see Supplementary data online, Figure S3a).

Discussion

The prognostic role of RV dysfunction in HF is well established, however, the significance of this relationship in specific subgroups and phenotypes of HF patients has not been well-validated. Hereby, we present our analysis that uses a large multicentre prospective cohort to comprehensively explore the prognostic role of CMR-derived RV systolic function in different subgroups of a HFREF cohort. Our results demonstrate that RVSD (defined as RVEF ≤45% by CMR) is prevalent amongst chronic HF patients (38.2%) and is an independent predictor of ACM and the composite outcome of HFH/ACM, even after adjusting for LV dysfunction and multiple other covariates. Several studies have evaluated the prognostic role of RVEF in HF patients using different modalities and cut-offs to define RVSD (Table 4).^{2,4,6,8–12,15,17–19}

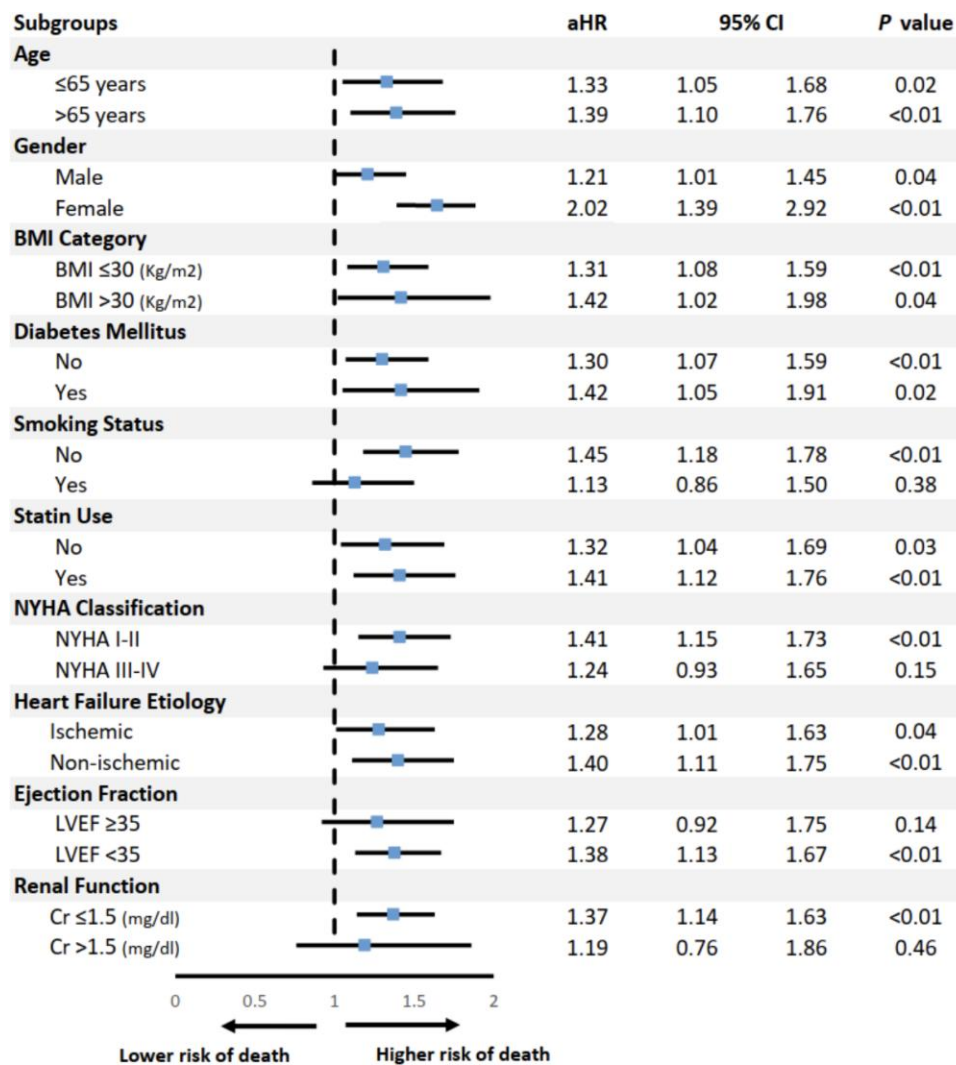


Figure 3 Subgroup analysis with aHRs for the composite outcome of ACM and/or HFHs in patients with RVSD (defined as EF <45%).

angina. This would likely have introduced selection bias in the subgroup analyses that partially explains why RVSD was not predictive of mortality in NYHA III/IV and ICM subgroups. Fourth, the observational nature of our data precludes the ability to make conclusion on causal association of RV dysfunction with clinical outcomes. In addition, external validation using a separate dataset is still required to verify the prognostic significance of RV parameters in HF patients. Finally, subgroup analysis is not a commonly adopted approach with observational data, however, epidemiologic studies suggest that subgroup-specific effects based on observational data could still be comparable to those performed in randomized clinical trials.²⁸

Conclusions

In patients with HFrEF, RV dysfunction is an independent predictor of poor clinical outcomes (HFH/ACM), irrespective of HF aetiology (ICM versus NICM). CMR-derived quantitative assessment of RV

function can provide valuable prognostic information and improve risk stratification of HF patients. However, the prognostic value of RVSD appears to have subgroup-specific effects; for instance, it was more pronounced in patients with NYHA I/II as opposed to those with NYHA III/IV, in patients with LVEF <35% as opposed to those with LVEF ≥35%, and in patients with normal renal function as opposed to those with renal dysfunction. These findings could reflect the importance of RV function in the early stages of HF, prior to the onset of clinical and hemodynamic deterioration.

Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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