

Sex differences in patients with cardiogenic shock

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Abstract

Aims Differences between female and male patients in clinical presentation, causes and treatment of cardiogenic shock (CS) are poorly understood. We aimed to investigate sex differences in presentation with and treatment of CS.

Methods and results We analysed data of 978 patients presenting with CS to a tertiary care hospital between October 2009 and October 2017. Multivariable adjusted logistic/Cox regression models were fitted to investigate the association between sex and clinical presentation, use of treatments and 30 day mortality.

Median age was 70 years (interquartile range 58–79 years), and 295 (30.2%) patients were female. After adjustment for multiple relevant confounders, female patients were more likely to be older [odds ratio (OR) 1.21, 95% confidence interval (CI) 1.02–1.42, $P = 0.027$], but other relevant presentation characteristics did not differ between both sexes. Despite the similar presentation, female patients were less likely to be treated with percutaneous left ventricular assist devices (OR 0.78, 95% CI 0.64–0.94, $P = 0.010$), but more likely to be treated with catecholamines (OR 1.21, 95% CI 1.02–1.44, $P = 0.033$) or vasopressors (OR 1.26, 95% CI 1.05–1.50, $P = 0.012$). A 30 day mortality risk in female patients was as high as in male patients (hazard ratio 1.08, 95% CI 1.00–1.18, $P = 0.091$).

Conclusions In this large, contemporary cohort, clinical presentation was comparable in female and male patients, and both sexes were associated with a comparably high mortality risk. Nevertheless, female patients received different treatment for CS and were most importantly less likely to be treated with percutaneous left ventricular assist devices.

Keywords Cardiogenic shock; Sex-related differences; Heart failure

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Introduction

Cardiogenic shock (CS) is the most severe form of acute heart failure. The main pathophysiology of CS is low cardiac output, which leads to tissue hypoperfusion, multi-organ failure and ultimately death. Although several attempts have been made in the last years to develop new treatments for CS, the mortality rate in this patient population is still high, 50–60%.¹ Inotropes, once considered to be the cornerstone of CS treatment, increase myocardial oxygen demand and are therefore associated with poor outcomes in CS.² As a consequence, active mechanical circulatory support with percutaneous left ventricular assist devices (pLVADs) and veno-arterial extracorporeal membrane oxygenation (va-ECMO) have been

increasingly used to treat CS in the past years. However, observational data indicate that these devices might not improve outcomes and could even increase risk of severe complications.^{3–6}

The high mortality risk of CS requires research efforts to understand the disease and its risk factors, with the ultimate aim to improve prognosis. Based on the overall observation of sex differences in clinical presentation, use of treatments, and outcomes in other cardiovascular diseases such as coronary artery disease, myocardial infarction, and heart failure,^{7,8} we hypothesized that there are relevant sex differences in CS, too. Improving the understanding of sex differences might facilitate the development of successful treatment strategies and conduction of clinical trials in this field.

Hence, the primary aim of this study was to investigate sex differences in clinical presentation, use of treatments, and outcomes between female and male patients in CS.

Material and methods

Study population

The present study considered patients with CS treated at the University Heart and Vascular Center Hamburg/University Clinic Hamburg-Eppendorf between October 2009 and October 2017. To identify eligible patients, the claims database was scanned for the International Classification of Diseases-10 code of CS (R.57). Hereafter, every identified case was checked based on electronic case records to validate the diagnosis of CS. Baseline data including known comorbidities upon presentation, laboratory analyses directly after presentation, use of treatments during hospital stay and in-hospital follow-up, and all-cause mortality were collected in a dedicated database.

In regard to va-ECMO use, standard cannulation included an arterial cannula size of 15–17 French and a venous cannula size of 21–23 French, although exact cannula size per patient was not recorded in this database. In regard to pLVAD use, the Impella CP® (Abiomed, Danvers, MA, USA) was predominantly used per standard operating procedure, with few exceptions of Impella 2.5® use (exact device type not recorded in this database).

This study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee. As this was a retrospective analysis of anonymized data, the need for an informed consent was waived by the local ethics committee.

Statistical analysis

Continuous variables are shown as median (25th percentile, 75th percentile); binary variables are shown as absolute and relative frequencies. Mann–Whitney test was used to compare continuous variables and χ^2 test was used to compare binary variables.

To enable multivariable analyses including all observations, missing data were handled by chained-equation multiple imputation (50 imputed data sets; R package mice). Except acute heart failure, other cause of CS, C-reactive protein, diastolic blood pressure, creatinine kinase, high-sensitive troponin T, all the variables shown in *Table 1*, as well as use of catecholamines, vasopressors, va-ECMO, and pLVAD were used for the multiple imputation.

To analyse differences in presentation characteristics between both sexes, a multivariable-adjusted logistic regression model with sex as the dependent variable and selected

presentation characteristics as independent variables was fitted (variables are shown in *Figure 1*).

To analyse the association between sex and use of selected treatments (catecholamines, vasopressors, va-ECMO, or pLVAD), a logistic regression model with the respective treatment as the dependent variable and sex as the independent variable was fitted, adjusted for age, prior cardiac arrest and time to return of spontaneous circulation, shock index (heart rate divided by systolic blood pressure) ≥ 1 , baseline lactate, and baseline pH. These variables were selected based on clinical and scientific knowledge.^{9–12}

To analyse the association between sex and outcome, a Cox regression model with 30 day in-hospital mortality as the dependent variable and sex as the independent variable was fitted, adjusted for the same variables as mentioned earlier. Median follow-up time was estimated by the reverse Kaplan–Meier estimator. Survival curves were produced using the Kaplan–Meier method. Additionally, to investigate the interaction between sex and the Society for Cardiovascular Angiography and Intervention CS classification (SCAI CS classification) as well as with the cause of CS, an interaction term was added to the Cox regression model described earlier. Variables used for the adjustment of the Cox and the logistic regression models described earlier were selected based on clinical and scientific knowledge.

All analyses were performed with R statistical software version 3.6.0; a *P* value below 0.05 was considered statistically significant. Change in continuous variables was modelled as change per standard deviation for all regression models.

Results

Overall study cohort

Baseline characteristics for the overall study cohort and divided by sex are shown in *Table 1*. In this cohort, 978 patients with CS were included. Less than one-third of the cohort were female (*N* = 293, 30.2%). In the unadjusted analysis, several baseline characteristics were distributed unequally between female patients and male patients; e.g. female patients were older (73.0 years vs. 69.0 years, *P* < 0.001), were less frequent smokers (20.1% vs. 34.8%, *P* < 0.001), presented less frequently with acute myocardial infarction (18.4% vs. 27%, *P* = 0.006), but more frequently with acute heart failure (32.2% vs. 25.5%, *P* = 0.037). Additionally, female patients presented more frequently in SCAI Class E, without significant differences in regard to the other classes of the SCAI CS classification.

Table 1 Baseline characteristics of all patients and divided by sex

	All (N = 978)	Missing (%)	Female patients (N = 295)	Male patients (N = 683)	P value
Demographics					
Age (years)	70.0 (58.0, 79.0)	0	73.0 (61.0, 80.0)	69.0 (57.0, 78.0)	<0.001
Cardiovascular risk factors					
BMI (kg/m ²)	24.7 (24.2, 28.3)	23.0	24.6 (23.0, 28.8)	24.7 (24.2, 28.2)	0.003
BSA (m ²)	1.96 (0.23)	23.0	1.80 (0.22)	2.03 (0.20)	<0.001
Smoking No. (%)	295 (30.3)	<0.01	59 (20.1)	236 (34.8)	<0.001
Arterial hypertension No. (%)	484 (49.8)	<0.01	146 (49.8)	338 (49.8)	1.000
Hypercholesterinaemia No. (%)	98 (10.1)	<0.01	25 (8.5)	73 (10.8)	0.350
Diabetes mellitus No. (%)	260 (26.7)	<0.01	78 (26.6)	182 (26.8)	1.000
Chronic kidney disease No. (%)	174 (17.9)	<0.01	53 (18.1)	121 (17.8)	0.990
Prior myocardial infarction No. (%)	237 (24.4)	<0.01	54 (18.4)	183 (27.0)	0.006
Prior stroke No. (%)	95 (9.8)	<0.01	36 (12.3)	59 (8.7)	0.110
Presentation					
Cause of cardiogenic shock		0.0			
Acute myocardial infarction No. (%)	473 (48.4)		123 (41.7)	350 (51.2)	0.008
Acute heart failure No. (%)	269 (27.5)		95 (32.2)	174 (25.5)	0.037
Other No. (%)	242 (24.7)		82 (27.8)	160 (23.4)	0.170
CPR No. (%)	567 (58.0)	<0.01	157 (53.2)	410 (60.1)	0.053
Time until ROSC (min)	20.0 (10.0, 45.0)	18.3	20.0 (8.0, 36.2)	21.5 (10.0, 45.0)	0.110
Refractory cardiac arrest No. (%)	116 (28)	15.8	32 (27.1)	84 (28.4)	0.890
Mechanical ventilation No. (%)	664 (68.2)	<0.01	193 (65.4)	471 (69.5)	0.240
Ejection fraction		20.1			
Preserved No. (%)	134 (17.2)		53 (22.7)	81 (14.8)	0.009
Mid-ranged No. (%)	127 (16.3)		34 (14.6)	93 (17.0)	0.470
Reduced No. (%)	520 (66.5)		146 (62.7)	374 (68.2)	0.150
SCAI CS classification		2.0			
SCAI class B	31 (3.2)		22 (3.3)	9 (3.1)	0.999
SCAI class C	415 (43.3)		286 (42.7)	129 (44.8)	0.590
SCAI class D	327 (34.1)		218 (32.5)	109 (37.8)	0.130
SCAI class E	185 (19.3)		144 (21.5)	41 (14.2)	0.012
Haemodynamics					
Systolic blood pressure (mmHg)	104.0 (85.0, 126.0)	8.0	100.0 (83.0, 126.1)	105.0 (85.0, 126.0)	0.650
Diastolic blood pressure (mmHg)	60.0 (47.7, 78.0)	8.3	60.0 (47.9, 77.1)	61.0 (47.2, 78.0)	0.510
Shock index ≥ 1 No. (%)	307 (35.1)	10.5	105 (39.2)	202 (33.3)	0.110
Heart rate (bpm)	90.0 (71.0, 110.0)	7.0	90.0 (73.0, 113.0)	89.0 (70.0, 109.0)	0.130
Laboratory					
Lactate (mmol/L)	4.0 (2.0, 8.0)	10.0	4.0 (2.0, 8.3)	4.0 (2.0, 8.0)	0.620
pH	7.3 (7.2, 7.4)	6.5	7.3 (7.2, 7.4)	7.3 (7.1, 7.4)	0.710
calculated GFR (ml/min)	42.8 (28.5, 58.9)	2.9	38.4 (25.5, 57.8)	43.9 (28.9, 59.7)	0.063
ASAT (U/l)	122.0 (47.0, 381.3)	14.4	124.0 (49.8, 328.8)	120.0 (46.0, 411.3)	0.720
CK total (U/l)	207.5 (101.9, 681.2)	7.0	198.0 (89.0, 721.3)	214.0 (109.0, 672.7)	0.180
Troponin T (pg/ml)	221.5 (54.9, 1410.0)	16.4	246.0 (58.0, 1379.3)	211.0 (53.0, 1450.3)	0.750
CRP (mg/l)	16.0 (5.0, 72.0)	7.0	21.0 (6.0, 77.7)	15.0 (5.0, 69.7)	0.057

ASAT, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CK, creatine kinase; CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; ROSC, return of spontaneous circulation; SCAI CS classification, Society for Cardiovascular Angiography and Intervention cardiogenic shock classification; calculated GFR, calculated glomerular filtration rate.

Continuous FV (25th, 75th percentile), binary variables as absolute and relative frequencies. The P value given is for the Mann–Whitney test or the χ^2 test.

Presentation characteristics

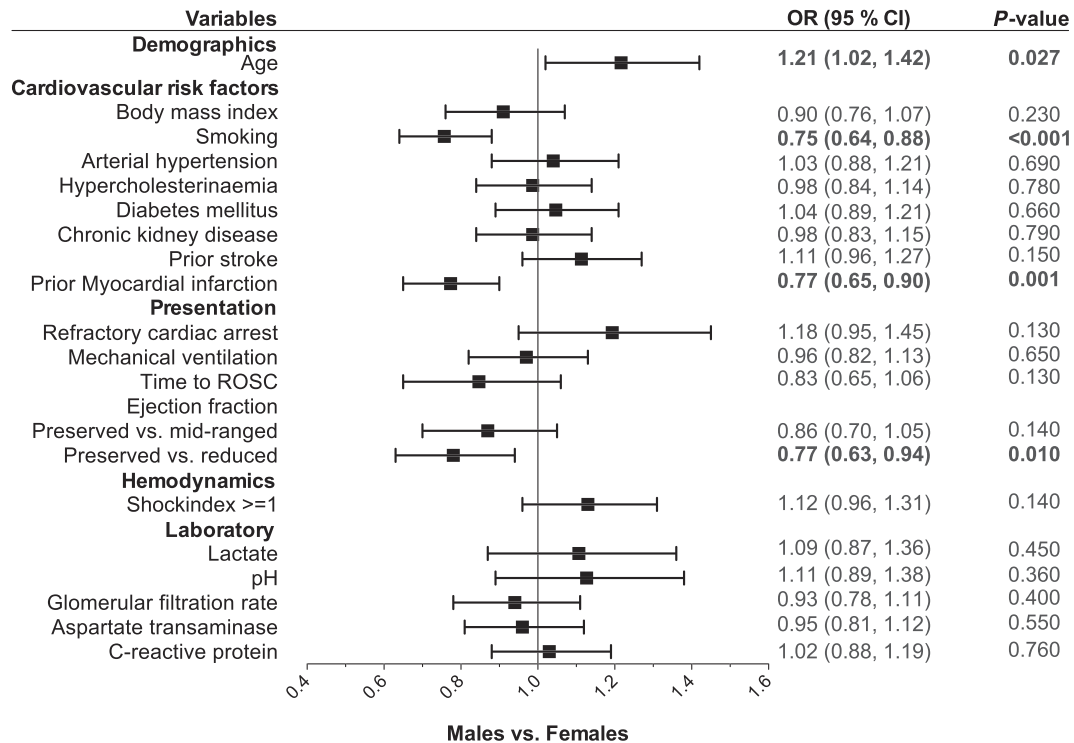
As baseline characteristics are unadjusted, we used a multi-variable adjusted logistic regression model to identify differences in clinical presentation between female and male patients (Figure 1). In the adjusted model, female patients presenting with CS were more likely to be older than males [odds ratio 1.21, 95% confidence interval (CI) 1.02, 1.42; $P = 0.027$], were less likely to be smokers (odds ratio 0.75, 95% CI 0.64, 0.88; $P < 0.001$), less likely to have had a prior myocardial infarction (odds ratio 0.77, 95% CI 0.65, 0.90; $P = 0.001$), and less likely to present with a reduced ejection

fraction (odds ratio 0.77, 95% CI 0.63, 0.94; $P = 0.01$). However, other cardiovascular risk factors and factors related to CS severity (e.g. lactate, pH, cardiac arrest, and shock index) were not significantly different between both sexes.

Use of treatments during cardiogenic shock

Patients with CS can receive both pharmacological therapy and mechanical circulatory support. In total, more pharmacological therapy in the form of catecholamines and vasopressors was applied in both sexes compared with device

Figure 1 Presentation characteristics of patients divided by sex. Multivariable adjusted logistic regression model for sex (female vs. male) as the dependent variable and all shown baseline characteristics as independent variables. Odds ratios (ORs) are shown on the x-axis. CI, confidence interval; ROSC, return of spontaneous circulation.



therapy. In our analysis, 764 (78.3%) patients were treated with catecholamines, 701 patients (74.3%) with vasopressors. Of the patients, 256 (26.2%) received va-ECMO, and 162 patients (16.6%) were treated with pLVAD. In both sexes, the use of va-ECMO in patients with CS increased from 2010 on and peaked in 2016, whereas the use of pLVAD started to increase later, in 2012, but also peaked in 2016 (*Figure 3*). In the multivariable adjusted logistic regression analysis, female patients were more likely to be treated with catecholamines (odds ratio 1.21, 95% CI 1.02, 1.44; $P = 0.033$) and vasopressors (odds ratio 1.26, 95% CI 1.05, 1.50; $P = 0.012$), but less likely to be treated with pLVAD (odds ratio 0.78, 95% CI 0.64, 0.94; $P = 0.01$) (*Figure 2*). The likelihood of treatment with va-ECMO was not significantly different between both sexes.

Outcome

Cumulative incidence curves for mortality are shown in *Figure 4*. During a median follow-up time of 26 days (95% CI 24; 28 days), 547 deaths (55.9%) occurred in the overall cohort, which corresponds to a survival probability of 38% (95% CI 35–42%) after 30 days. Survival probability in female

patients only was 36% (95% CI 30–43%) and the survival probability in male patients only was 39% (95% CI 35–43%; $P = 0.091$).

In the multivariable adjusted Cox regression model, female sex was associated with a similar risk of 30 day all-cause mortality as male sex, although there was a trend towards a higher mortality risk in female patients [hazard ratio (HR) 1.08, 95% CI 1.00–1.18; $P = 0.065$].

Mortality risk was comparable between female and male patients across the strata of the SCAI CS classification: SCAI Class C vs. B HR 1.03 (95% CI 0.54–1.96) in female patients vs. HR 1.99 (95% CI 0.62–6.34) in male patients (interaction $P = 0.33$); SCAI Class D vs. B HR 1.10 (95% CI 0.58–2.11) in female patients vs. HR 3.24 (95% CI 1.02–10.31) in male patients (interaction $P = 0.11$); and SCAI Class E vs. B HR 2.06 (95% CI 1.07–3.94) in female patients vs. HR 4.95 (95% CI 1.51–16.22) in male patients (interaction $P = 0.20$).

Similarly, the mortality risk was not different between female and male patients in regard to the underlying cause of CS: ischaemic CS (with acute myocardial infarction) vs. non-ischaemic CS (without acute myocardial infarction) HR 0.82 (95% CI 0.66–1.01) in female patients vs. HR 0.65 (95% CI 0.47–0.90) in male patients (interaction $P = 0.24$).

Figure 2 Use of therapies during cardiogenic shock in female and male patients. Logistic regression model for sex (female vs. male patients) as the dependent variable and all shown therapies as independent variables. Additionally, all models were adjusted for age, sex, prior cardiac arrest, time to return of spontaneous circulation, shock index ≥ 1 , baseline lactate, and baseline pH. Odds ratios (ORs) are shown on the x-axis. CI, confidence interval; ECMO, veno-arterial extracorporeal membrane oxygenation; pLVAD, percutaneous left ventricular assist device.

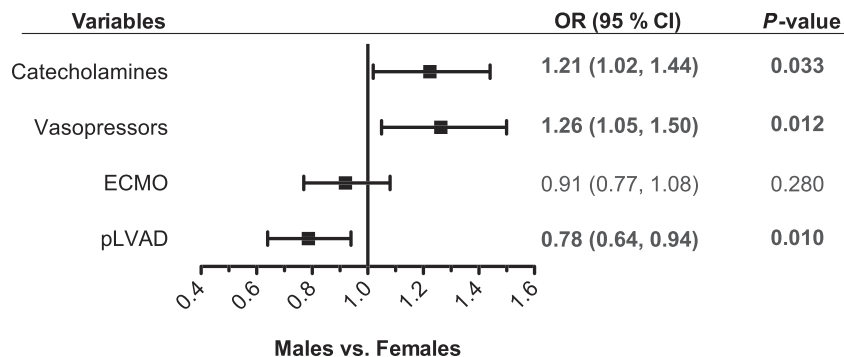
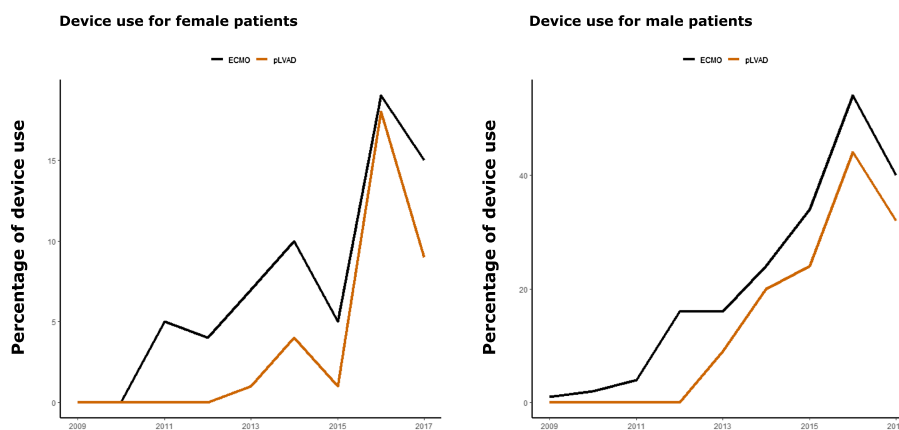


Figure 3 Device use in female and male patients over time. pLVAD: percutaneous left ventricular assist device; va-ECMO: veno-arterial extracorporeal membrane oxygenation.



Discussion

The main findings of this study are as follows:

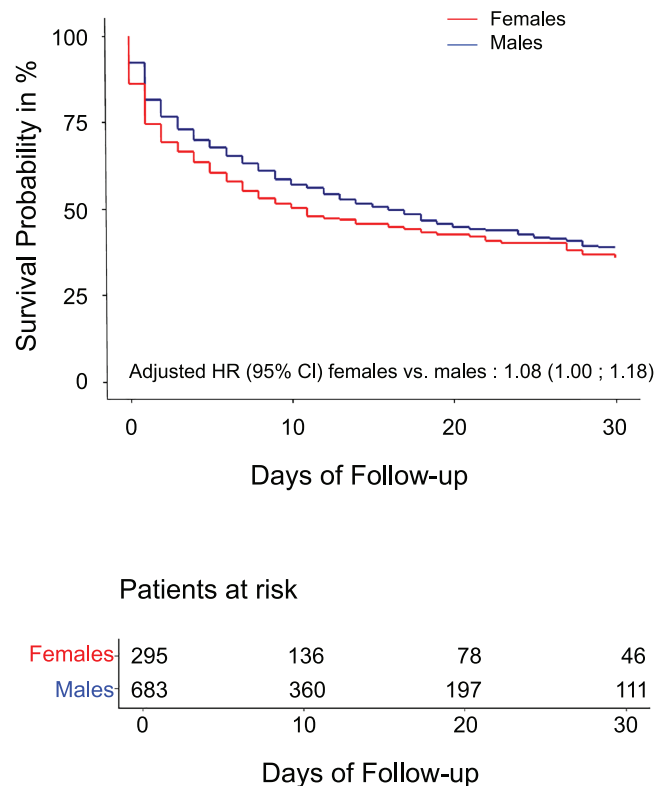
- 1 Female patients presenting with CS were older than male patients, but there were no relevant differences in factors relating to shock severity;
- 2 Mortality risk in CS was comparably high in female and male patients, even after adjustment for relevant confounders;
- 3 Treatment of CS differed significantly between both sexes, as female patients were less likely to be treated with pLVAD and more likely to be treated with catecholamines or vasopressors.

These findings are of major importance, as they reveal marked sex differences in the use of treatment for CS, despite a comparably high-risk profile.

Sex-differences in clinical presentation and outcome

A substudy of the IABP-SHOCK II-trial in patients with CS complicating myocardial infarction showed that female patients were older than male patients and revealed a worse cardiovascular risk profile compared with male patients. Significant sex-related differences in therapy and short-term outcome could not be observed.¹³ In our study, female patients were also older than male patients; they were less likely to be active smokers, but other cardiovascular risk factors did not differ significantly. We also observed a similar outcome with a high risk of 30 day mortality in both sexes, which was consistent across all classes of the SCAI CS classification. In another study of CS caused by acute myocardial infarction, Abdel-Qadir *et al.* also showed that female patients presenting with CS tend to have a higher age than male patients and also reported comparable mortality rates for both sexes.⁸

Figure 4 Survival curves divided by sex. Survival curves for 30 day mortality in female and male patients presenting with cardiogenic shock. The numbers of patients at risk are provided under the figure. HR, hazard ratio.



In a substudy of the CULPRIT-SHOCK trial (The Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock), sex did not influence mortality and renal failure, although female patients presented with a different risk factor profile.¹⁴ Importantly, these three studies focused exclusively on patients with CS caused by acute myocardial infarction. However, acute myocardial infarction only accounts for about 50% of CS cases, and the other 50% is caused by non-ischæmic causes such as acute decompensated heart failure.¹⁵ This is of major importance, as non-ischæmic causes of CS call for a different treatment approach and are associated with a worse prognosis than CS caused by acute myocardial infarction.¹⁵ Our study enrolled an unselected cohort of CS patients, including cases caused by acute myocardial infarction as well as non-ischæmic CS and thus allows us to generalize the observation on sex differences in CS to the overall CS population.

Use of treatments

It is known that there are differences between female and male patients in therapy of cardiovascular diseases. Female patients are less likely to be treated with device therapy or interventional therapy, for example, cardiac

resynchronization therapy,¹⁶ although female patients were demonstrated to derive greater therapeutic benefit from cardiac resynchronization therapy compared with male patients.¹⁷ Similarly, female patients are less likely to be treated with implantable cardioverter defibrillators.¹⁸

Our study identified a similar pattern of underuse of device therapies in female patients presenting with CS. Although female patients had a similar risk profile as male patients presenting with CS, and although mortality risk was comparable between both sexes, female patients received a different therapy for CS. They were more likely to be treated with catecholamines or vasopressors, but were less likely to undergo pLVAD support. Pharmacological therapies are important in treatment of CS. Catecholamines and vasopressors such as dobutamine and norepinephrine show a positive effect on cardiac inotropy and can help to maintain sufficient blood pressure. However, they also increase myocardial oxygen demand, increase cardiac afterload, but seem not to improve outcomes in patients with CS.^{19,20} Recently, active mechanical circulatory support with pLVAD and va-ECMO has been proposed as an alternative to catecholamines/vasopressors for the treatment of CS. This has led to an increasing use of these devices over the past years.^{2,3,21} Initial observational studies did not show a survival benefit associated with the use of pLVAD/va-ECMO.^{4-6,22} However, these devices are still

considered as potentially beneficial for the treatment of CS from a pathophysiological point of view. Hence, several randomized controlled trials are currently ongoing, aiming to clarify the efficacy and safety of these devices.^{23,24} These trials might also help to identify relevant selection criteria for these devices, for example, help physicians to identify patients most likely to benefit from device-based treatment.

A potential reason for the underuse of pLVAD in female patients might be their smaller body and thus vessel size, as indicated by a significant difference in body surface area in this analysis. As pLVAD require a large bore vessel access, physicians might be reluctant to implant such devices in female patients with smaller arteries; being worried about a higher complication risk. Additionally, the higher likelihood of heart failure with preserved ejection fraction with presumably smaller left ventricular cavities in female patients might be another explanation for the less frequent use of pLVAD; as physicians might be less inclined to use these devices for concerns regarding their efficacy in this setting (e.g. suction phenomena due to smaller left ventricular cavities). Importantly, this does not indicate that female patients received less ideal treatment than male patients, especially as the mortality risk was comparable between both sexes. However, this highlights a potential sex-specific selection bias in the use of pLVADs for the treatment of CS and indicates that these devices might not be optimized for the use in female patients. Currently, the available data on mechanical circulatory support in CS do not indicate any sex-specific difference in a potential benefit from pLVAD. However, the one-size-fits-all design of current device platforms might prevent detection of such differences. As an example, optimized device platforms with cannulas specifically designed for female patients might reduce device-associated complications. As a consequence, this could unmask a potential benefit from mechanical circulatory support in females. Ultimately, concerns regarding anatomical disadvantages of female patients might be met by adapting the design of these devices, for example, by reducing the size of the required bore vessel access or by adjusting the inflow cannula design, which could then improve its overall use.

Limitations

Strengths of this study include the large, well-characterized and contemporary CS cohort with data on clinical presentation, use of treatment, and outcomes. The cause of CS was not limited to ischaemic aetiology, as patients with non-ischaemic aetiology were included, too.

Its main limitation is its retrospective, observational design, which does not allow us to rule out residual or unmeasured confounding. The use of International Classification of Diseases-10 codes for patients with CS might have changed over time and could have impacted the results.

The study is based on a cohort from a single hospital, which might limit generalizability to other hospitals or health care systems. Additionally, haemodynamic data (e.g. right heart catheterization) were not available for this study and could thus not be analysed; and its absence might have also influenced the treating physicians choice of therapies.

Conclusions

In this large, contemporary cohort of patients presenting with CS, there were no relevant differences in clinical presentation and shock severity between female and male patients, and mortality risk was comparable for both sexes. Despite these similarities, female patients received different treatment for CS, for example, they were more likely to be treated with catecholamines or vasopressors, but less likely to be treated with pLVAD. Smaller vessel size and a higher prevalence of preserved ejection fraction might have contributed to this sex-specific treatment selection; and concerns regarding anatomical disadvantages of female patients might be met by adapting the design of these devices.

Conflict of interest

Dr Beer reports honoraria from Siemens Healthineers, outside the submitted work.

Dr Seiffert reports non-financial support from Abbott Vascular, personal fees from Abiomed, personal fees from AstraZeneca, personal fees from Bayer Healthcare, non-financial support from Biotronik, personal fees from Boehringer Ingelheim, personal fees and non-financial support from Boston Scientific, personal fees from Bristol-Myers Squibb, non-financial support from Edwards Lifesciences, non-financial support from Nicolai Medizintechnik, non-financial support from OrbusNeich Medical, grants and personal fees from Philips, personal fees from Medtronic, and personal fees from Amgen, outside the submitted work.

Prof Schnabel reports personal fees from BMS/Pfizer outside the submitted work.

Prof Blankenberg reports grants and personal fees from Abbott Diagnostics, grants and personal fees from Bayer, grants and personal fees from Siemens, grants from Singulex, grants and personal fees from Thermo Fisher, personal fees from Abbott, personal fees from AstraZeneca, personal fees from Amgen, personal fees from Medtronic, personal fees from Pfizer, personal fees from Roche, personal fees from Siemens Diagnostics, and personal fees from Novartis, outside the submitted work.

Prof Kirchhof receives research support for basic, translational, and clinical research projects from the European Union, British Heart Foundation, Leducq Foundation, Medical

Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last 3 years. He is also listed as an inventor on two patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

Dr Schrage reports personal fees from AstraZeneca, outside the submitted work.

Prof Westermann reports personal fees from AstraZeneca, personal fees from Bayer, personal fees from Novartis,

personal fees from Berlin-Chemie, and personal fees from Medtronic, outside the submitted work.

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