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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Gender differences and outcomes in left ventricular assist device support: The European Registry for Patients with Mechanical Circulatory Support

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KEYWORDS:
gender differences;
ventricular assist device;
adverse events;
survival;
EUROMACS

BACKGROUND: Despite the increasing use of ventricular assist devices (VADs), gender differences in indications, hemodynamics, and outcome are not well understood. We examined gender differences and gender-specific predictors for perioperative outcome in patients on ventricular support.

METHODS: Multicenter data of 966 patients (median age 55 years, 151 women) from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) were analyzed. Median follow-up was 1.26 years.

RESULTS: At the time of VAD implantation, women were more often in an unstable condition (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] profile 1 and 2) (51.7% vs 41.6% in men), experiencing significantly more often major bleeding ($p = 0.0012$), arrhythmias ($p = 0.022$), and right ventricular (RV) failure ($p < 0.001$) with need for additional RV support. The survival of women on isolated LVAD support was significantly worse (1-year survival 75.5% vs 83.2% in men). Age-adjusted Cox regression analyses showed significant associations with mortality for preoperative inotropic therapy, percutaneous mechanical support, INTERMACS profile 1 and 2, RV dysfunction, major bleeding, cerebral bleeding, ischemic stroke, and RV failure. In women, pump thrombosis was more strongly related with mortality compared to men, while the direction of the association of renal dysfunction with mortality was different for women and men (p-value interaction 0.028 and 0.023, respectively).

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2017.06.016

CONCLUSIONS: Women and men differ in perioperative hemodynamics, adverse events, and mortality after VAD implantation. A gender-dependent association of pump thrombosis with mortality was seen. The impact on treatment practice needs to be shown.
J Heart Lung Transplant ▮▮▮▮;▮:▮▮▮–▮▮▮

Due to the growing organ shortage and technical progress, ventricular assist devices (VADs) are gaining importance in the treatment of end-stage heart failure (HF). Women and men differ in terms of HF etiology, diagnosis, prognosis, and treatment.[1] Women have a higher HF incidence than men.[2] Women are hospitalized more frequently and die more often than men from the consequences of HF.[3] Although women are hospitalized in more advanced states of decompensated HF,[4] VAD placement is far less likely.[5,6] At time of implantation, women are more frequently in cardiogenic shock (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] level 1)[7] and receive devices with smaller pump sizes.[8] After VAD implantation, women require longer ventilatory and inotropic support resulting in prolonged intensive care stays.[7] Furthermore, women have a higher risk for neurologic complications and perioperative right ventricular (RV) failure requiring additional RV support.[6,7,9] However, there is contradictory evidence regarding gender-specific outcome.[4–7] Therefore, in the largest European study sample of patients undergoing mechanical circulatory support to date, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), we aimed to further evaluate gender differences in adverse events. Additionally, we tried to identify gender-specific predictors for survival of women and men undergoing VAD implantation.

Methods

Study population

Between January 2011 and June 2014, 966 patients were prospectively enrolled into EUROMACS, an online database collecting anonymized data of demographics, device implantation, and long-term follow-up of patients with ventricular support.[10] At the present time, more than 50 European and non-European centers from 15 countries are involved. Preimplantation data regarding patient characteristics, social situation, HF medication at admission, preoperative blood values, primary cardiac diagnosis, and INTERMACS profile are recorded. Data on the following device strategies are available: bridge to recovery, bridge to transplantation (possibly bridged, currently listed), destination therapy, rescue therapy, and others. Hemodynamic data from echocardiography and right heart catheter, intraoperative characteristics, and procedural characteristics are stored. Adverse events, including ischemic strokes, cerebral bleeding, arrhythmias, pump thrombosis, major bleeding, major infections, RV failure, and renal and hepatic dysfunction are indicated. The definition of adverse events in EUROMACS corresponds to the INTERMACS definition.[10,11] Every follow-up visit and all adverse events, including death of a patient, are reported. All contributing centers were contacted to confirm correctness of data by the end of follow-up. Pediatric patients were excluded.

Statistical methods

After exclusion of pediatric patients and 1 patient with missing device information, the data set consisted of 966 patients undergoing long-term VAD support. Patients receiving right ventricular assist device (RVAD), biventricular assist device (BIVAD), total artificial heart, CircuLite Synergy, HeartWare MVAD, or not-specified device brands were excluded from all survival analyses (including survival and incidence estimation and Cox regression analyses).

Available-case analyses, also known as pairwise deletion, were used. For each computation, only cases without missing values on the variables involved in that particular analysis were used. For continuous variables, median (25th, 75th percentile) is given, and Mann-Whitney test is performed. For categorical variables, absolute and relative frequencies are given, and Fisher exact test is performed. Gender-specific survival curves on LVAD and temporary RVAD therapy were drawn using the Kaplan-Meier method. The equality of the survival curves was tested using the log-rank test. Cumulative incidence functions were computed for the outcomes transplantation, death, and recovery for each gender using a competing risks approach. Equality of these functions was tested by Gray's test. Incident gender-specific adverse event rates are given. We performed Cox regression analyses to examine the extent to which selected hemodynamic parameters (analyses shown for preoperative inotropic therapy, percutaneous mechanical circulatory support, INTERMACS profile 1 and 2, and RV function) and adverse events (analyses shown for major bleeding, cerebral bleeding, ischemic stroke, pump thrombosis, RV failure, and renal dysfunction) were associated with survival for each gender. All Cox models were adjusted for age, gender, and LVAD brand. Each adverse event was used as a time-dependent covariate in the respective Cox model. Besides the predictor of interest (hemodynamic parameter, adverse event), the models include age, device type, gender, and an interaction term for gender and the predictor of interest. Cox models that do not include the aforementioned interaction term were also computed. Confidence intervals (CI) and p-values for the variable of interest were computed using the methods described by Figueiras et al.[12] Analyses were performed using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

Results

Gender-specific preoperative characteristics

Selected baseline characteristics of the study sample are presented in Table 1 (for further baseline characteristics see Table S1a; missing value information is provided in Table S1b, available in the online version of this article at www.jhltonline.org). Patients (n = 966) (median age 55 years, 151 [15.6%] women, 84% European origin)

Table 1 Selected General Characteristics of the Study Sample

Variable	Men (n = 815)	Women (n = 151)	*p*-value
Age, years	56 (46.2, 62)	53 (40.3, 62)	0.088
Body surface area, m^2	2.0 (1.9, 2.1)	1.7 (1.6, 1.9)	<0.001[a]
Diabetes, *n* (%)	200 (25.2)	38 (25.7)	0.92
Ever smoker, *n* (%)	294 (69.2)	25 (34.7)	<0.001[a]
Chronic obstructive pulmonary disease, *n* (%)	88 (11.1)	10 (6.8)	0.14
Symptomatic peripheral vascular disease, *n* (%)	61 (7.7)	5 (3.4)	0.077
Carotid artery disease, *n* (%)	22 (3.2)	3 (2.2)	0.78
Positive history of neurologic event, *n* (%)	89 (11.6)	16 (10.7)	0.89
Dialysis, *n* (%)	20 (2.5)	5 (3.3)	0.58
Ultrafiltration, *n* (%)	49 (6.1)	6 (4)	0.44
Intubation, *n* (%)	118 (14.7)	26 (17.3)	0.39
Currently on intravenous inotropes, *n* (%)	501 (65.9)	105 (71.4)	0.21
Intra-aortic balloon pump, *n* (%)	97 (12.1)	27 (18)	0.063
Extracorporeal membrane oxygenation, *n* (%)	75 (9.4)	19 (12.7)	0.23
Primary diagnosed cardiomyopathy, *n* (%)			<0.001[a]
Congenital	12 (1.6)	2 (1.4)	1.0
Ischemic	369 (47.8)	39 (26.7)	<0.001[a]
Dilated	367 (47.5)	97 (66.4)	<0.001[a]
Restrictive	5 (0.6)	4 (2.7)	0.040[a]
Valvular	19 (2.5)	4 (2.7)	0.78
INTERMACS patient profiles, *n* (%)			0.30
1 and 2: unstable	334 (41.6)	77 (51.7)	0.025[a]
1: critical cardiogenic shock	90 (11.2)	24 (16.1)	0.099
2: progressive decline	244 (30.4)	53 (35.6)	0.21
3: stable but inotrope dependent	253 (31.5)	37 (24.8)	0.12
4: resting symptoms	177 (22.1)	32 (21.5)	0.91
5: exertion intolerant	28 (3.5)	3 (2)	0.46
6: exertion limited	7 (0.9)	0 (0)	0.60
7: advanced NYHA class III	3 (0.4)	0 (0)	1.0
Current device strategy, *n* (%)			0.80
Bridge to recovery	6 (0.7)	0 (0)	0.60
Bridge to transplantation			
Possibly bridged	366 (45.6)	72 (48)	0.59
Currently listed	243 (30.3)	43 (28.7)	0.77
Destination therapy	148 (18.4)	27 (18)	1.0
Rescue therapy	32 (4)	8 (5.3)	0.5
Other	8 (1.0)	0 (0)	0.62
Preoperative blood values			
Creatinine, μmol/liter	106.0 (82.0, 141.0)	94.0 (70.0, 132.0)	0.0097[a]
Hemoglobin, g/dl	11.9 (10.2, 13.6)	11.0 (10.1, 12.7)	0.0081[a]
Total bilirubin, mg/dl	1.3 (0.8, 2.1)	1.3 (0.8, 2.2)	0.83
Platelet count, $\times 10^9$/liter	189.0 (138.0, 241.0)	196.0 (149.0, 256.0)	0.28

For continuous variables, median (25th percentile, 75th percentile) is given and Mann-Whitney test is performed. For categorical variables, absolute and relative frequencies are given, and Fisher exact test is performed. For additional variables, see Table S1 (available in the online version of this article at www.jhltonline.org).

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

[a]statistically significant.

underwent primary ventricular support (LVAD, $n = 790$; BIVAD, $n = 52$; LVAD with temporary RVAD, $n = 99$; isolated RVAD, $n = 10$; total artificial heart, $n = 15$). Ischemic cardiomyopathy was less frequent in women than in men, whereas prevalence of dilated cardiomyopathy was higher in women (Table 1). At the time of VAD implantation, women were more often in unstable condition (INTERMACS profile 1 or 2), although preoperatively no differences were seen in need for renal replacement therapy, ventilation, or percutaneous mechanical circulatory support.

Gender-specific intraoperative and postoperative characteristics

More women had moderate or severe mitral and tricuspid regurgitation but less aortic regurgitation resulting in less concomitant aortic valve replacement (Tables 2 and 3; additional hemodynamic parameters and procedural characteristics are given in Tables S2 and S3, available in the online version of this article at www.jhltonline.org). Choice of device brands differed between genders (Table 3). The HeartWare HVAD was significantly more often

Table 2 Selected Hemodynamic Parameters

	Men ($n = 815$)	Women ($n = 151$)	p-value
Heart rate, beats/min	86 (74, 99)	88 (74.2, 102.8)	0.20
Systolic blood pressure, mm Hg	100 (90, 110)	96 (86, 107.3)	0.11
Mitral regurgitation, *n* (%)			0.0075[a]
None/trivial	51 (7.4)/60 (8.7)	15 (12.0)/6 (4.8)	0.11/0.16
Mild	233 (33.7)	26 (20.8)	0.0046[a]
Moderate	225 (32.6)	49 (39.2)	0.15
Severe	122 (17.7)	29 (23.2)	0.17
Tricuspid regurgitation, *n* (%)			<0.001[a]
None/trivial	58 (8.5)/97 (14.2)	17 (13.4)/10 (7.9)	0.095/0.063
Mild	267 (39.1)	28 (22)	<0.001[a]
Moderate	175 (25.7)	41 (32.3)	0.13
Severe	85 (12.5)	31 (24.4)	<0.001[a]
Aortic regurgitation, *n* (%)			0.020[a]
None/trivial	345 (56.7)/123 (20.2)	77 (71.3)/15 (13.9)	0.0042[a]/0.15
Mild	96 (15.8)	15 (13.9)	0.77
Moderate	38 (6.2)	1 (0.9)	0.020[a]
Severe	7 (1.1)	0 (0)	0.6
Left ventricular ejection fraction, *n* (%)	20 (15, 24)	20 (15, 25)	0.15
Right ventricular function, *n* (%)			0.49
Normal/mild	128 (19.3)/151 (22.8)	29 (25.0)/26 (22.4)	0.17/1.0
Moderate/severe	267 (40.3)/117 (17.6)	45 (38.8)/16 (13.8)	0.84/0.35
Pulmonary artery systolic pressure, mm Hg	50 (39, 64)	48 (36, 57)	0.017[a]
Cardiac index, liter/min/m^2	1.4 (0, 2.1)	1.3 (0, 2.0)	0.40

For continuous variables, median (25th percentile, 75th percentile) is given, and Mann-Whitney test is performed. For categorical variables, absolute and relative frequencies are given, and Fisher exact test is performed. For additional variables, see Table S2 (available in the online version of this article at www.jhltonline.org).

[a]statistically significant.

implanted in women. Women needed more additional RV support. In women, longer postoperative ventilatory support and a trend towards a longer stay in the intensive care unit were reported.

Gender differences in adverse events

After a median follow-up of 1.26 years (range 0.03–50.73 months; median follow-up 1.3 years in men vs 1.2 years in women) and 987 patient-years, 309 deaths (247 among men and 62 among women) were reported. In women, more episodes of major bleeding (events per patient year [PY] 0.3 in women vs 0.14 in men, $p = 0.0012$) (Figure 1) were reported. Women had a higher incidence of arrhythmias (events per PY 0.08 in women vs 0.03 in men, $p = 0.022$) and RV failure (events per PY 0.11 in women vs 0.03 in men, $p < 0.001$). No differences in ischemic stroke (events per PY 0.08 in women vs 0.06 in men, $p = 0.36$) and cerebral bleeding (events per PY 0.03 in women vs 0.03 in men, $p = 0.84$) were observed (Figure 1).

Survival and predictors for mortality

Women receiving isolated left ventricular support showed a significantly worse overall survival (Figure 2). Survival of women receiving LVAD with temporary RVAD support was even worse but did not differ significantly from men (Figure 2). No gender differences in transplant rates were seen (Figure 3). Parameters mirroring hemodynamic compromise were shown to predict survival on VAD support. Preoperative inotropic therapy, percutaneous mechanical support, INTERMACS profile 1 and 2, and highly reduced RV function were related to mortality (Table S4, available in the online version of this article at www.jhltonline.org) with a significant gender interaction for the association of percutaneous mechanical circulatory support and mortality (Table 4). In a refining analysis, which included these variables in a single model, INTERMACS profile 1 and 2 and preoperatively highly reduced RV function were no longer associated with mortality in both genders (Table S5, available in the online version of this article at www.jhltonline.org).

Furthermore, several VAD-related adverse events were significantly related to mortality. After adjustment for age, gender, and device brand, major bleeding, cerebral bleeding, ischemic stroke, pump thrombosis, RV failure, and renal dysfunction were significantly associated with mortality in the overall cohort (Table S6, available in the online version of this article at www.jhltonline.org). In a refining analysis with gender interaction (Table 5), the associations persisted in women and men, with the exception of renal dysfunction in women. A significant gender interaction in the association of pump thrombosis with mortality was observed indicating a stronger association in women (Table 5). The associations remained statistically significant after further adjustment for body mass index, diabetes, systolic blood pressure, chronic obstructive pulmonary disease, and symptomatic peripheral vascular and carotid artery disease (analyses not shown).

Table 3 Selected Intraoperative and Procedural Characteristics

	Men ($n = 815$)	Women ($n = 151$)	p-value
Device brand, *n* (%)			<0.001[a]
Berlin Heart Excor	9 (1.1)	3 (2)	0.42
Berlin Heart Incor	7 (0.9)	1 (0.7)	1.0
CircuLite Synergy	4 (0.5)	0 (0)	1.0
Heart Assist 5	4 (0.5)	1 (0.7)	0.58
Thoratec HeartMate II	339 (42.9)	36 (24)	<0.001[a]
Thoratec HeartMate III	1 (0.1)	0 (0)	1.00
Thoratec PVAD	10 (1.3)	5 (3.3)	0.075
HeartWare HVAD	411 (52)	102 (68)	<0.001[a]
HeartWare MVAD	0 (0)	1 (0.7)	0.16
Jarvik 2000	1 (0.1)	0 (0)	1.0
Other	4 (0.5)	1 (0.7)	0.58
Device type, *n* (%)			0.0094[a]
BIVAD	41 (5)	11 (7.3)	0.24
LVAD, temporary RVAD	73 (9)	26 (17.2)	0.0034[a]
LVAD	677 (83.1)	113 (74.8)	0.021[a]
RVAD	9 (1.1)	1 (0.7)	1.0
Total artificial heart	15 (1.8)	0 (0)	0.15
Cardiopulmonary bypass time, minutes	90 (68, 122)	83 (63, 117)	0.036[a]
Valve replacement, *n* (%)			
Aortic valve	53 (44.5)	5 (20)	0.026[a]
Mitral valve	7 (5.9)	2 (8)	0.66
Tricuspid valve	67 (56.3)	19 (76)	0.076
LVAD flow, liter/min	4.9 (4.2, 5.5)	4.4 (3.7, 4.9)	<0.001[a]
Ventilation time, hours	48 (16.9, 192)	89.0 (24, 248.7)	0.0068[a]
Intensive care stay, days	10 (5, 23)	11.5 (6, 29.6)	0.064
Patients discharged to rehabilitation, *n* (%)	154 (20.8)	29 (20.7)	1.0

For continuous variables, median (25th percentile, 75th percentile) is given, and Mann-Whitney test is performed. For categorical variables, absolute and relative frequencies are given, and Fisher exact test is performed. For additional variables, see Table S3 (available in the online version of this article at www.jhltonline.org).

BIVAD, biventricular assist device; LVAD, left ventricular assist device; RVAD, right ventricular assist device.

[a]statistically significant.

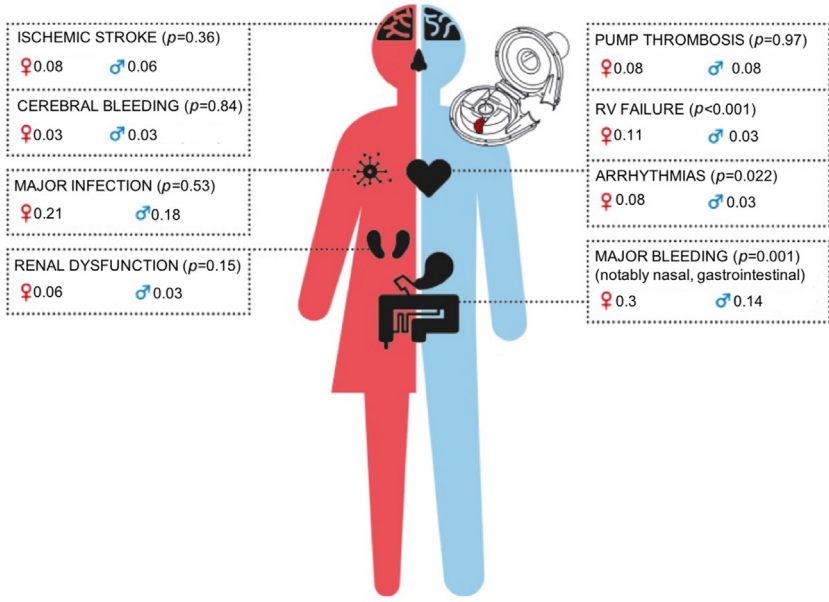
Discussion

We demonstrated significant gender differences not only in the perioperative period but also in the long-term course after VAD implantation. Women were shown to receive less VAD support despite a more critical HF state at admission. Both genders differed for implanted device types with implantation of smaller device pumps in women. Women required temporary or permanent RV support more often due to a higher incidence of RV failure. Overall survival in women was significantly worse.

In contrast to prior smaller studies with a comparatively low number of women,[4,6] our sample represents the largest European registry and one of the largest cohorts worldwide that permits the investigation of gender differences in long-term mechanical support. Compared with the earlier report on gender differences by Hsich et al[13] in INTERMACS, our study is characterized by a longer follow-up time after VAD implantation and by a higher rate of continuous-flow devices (HeartMate II and HeartWare HVAD). The latter have almost completely replaced pulsatile systems. Thus, our study mirrors current daily clinical practice with a state-of-the-art technology.

Gender-specific periprocedural characteristics

Despite a higher probability of hemodynamic compromise,[4,7] women still are less likely to receive assist device support.[4,5] Women are underrepresented in large multicenter trials as stated by the American College of Cardiology/American Heart Association 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.[14] Accordingly, women comprised only 15.6% of our study population, which is slightly lower than in comparable international registries such as INTERMACS. Whether this is due to European referral strategies or preferred device types cannot be answered by our data. Women presented significantly more often in INTERMACS level 1 and 2. This may be explained by 2 reasons: First, women are more likely to be transferred for VAD implantation in a later and more critical clinical state. Second, the smaller intrathoracic volume of women is not suited for larger pump sizes. We and others have shown that the smaller HeartWare HVAD pump was preferred in women.[8] Despite the more unstable condition at admission of women, there were no differences in inotropic therapy or percutaneous mechanical support. Consistent with prior reports,[7] women needed longer



Adverse events in the first 30 days after ventricular assist device implantation.

	Observed events Men	N available Men	Event % 1 month Men	Observed events Women	N available Women	Event % 1 month Women	*p*-value
Ischemic stroke	11	739	1.55	3	136	2.5	0.54
Cerebral bleeding	3	738	0.45	1	135	0.84	0.66
Major infection	33	737	4.74	7	136	5.52	0.68
Renal dysfunction	10	739	1.4	5	136	3.73	0.024
Pump thrombosis	17	737	2.41	4	136	3.22	0.59
Right ventricular failure	14	739	1.93	11	136	8.33	<0.001
Arrhythmias	8	739	1.13	5	136	3.82	0.016
Major bleeding	48	738	6.7	18	136	13.86	0.007

Adverse events after 30 days of ventricular assist device implantation.

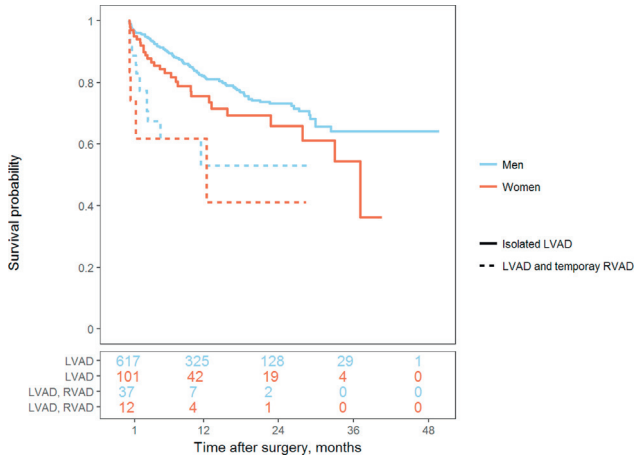
	Observed events Men	N available Men	Events per patient year Men	Observed events Women	N available Women	Events per patient year Women	*p*-value
Ischemic stroke	34	638	0.05	11	113	0.14	0.029
Cerebral bleeding	22	644	0.03	3	112	0.03	0.92
Major infection	106	644	0.19	18	108	0.26	0.60
Renal dysfunction	26	640	0.04	5	111	0.06	0.61
Pump thrombosis	50	634	0.08	8	111	0.09	0.85
Right ventricular failure	23	641	0.04	10	115	0.11	0.007
Arrhythmias	21	638	0.03	7	114	0.08	0.080
Major bleeding	92	617	0.16	24	108	0.32	0.021

Figure 1 Gender-specific adverse event rates. Events per patient year are given for women (red; $n = 136$) and men (blue; $n = 739$). Patients with RVAD, BIVAD, total artificial heart, CircuLite Synergy, HeartWare MVAD, and not-specified device brands were excluded from analysis.

ventilatory support. Women showed a trend towards a longer stay in the intensive care unit. Additionally, women and men differed in HF etiology. Ischemic cardiomyopathy is less frequent in women receiving VAD support,[6] which is explained by the fact that women have coronary artery disease less often than men.[15]

Gender-specific adverse events

In line with the report by Boyle et al,[16] who showed that women have a higher risk for bleeding complications on continuous-flow assist devices, women had a higher rate of major bleeding after VAD implantation in our cohort. The assumption that differences in blood coagulation or gender-specific pharmacokinetics and pharmacodynamics of anticoagulant medication are driving the bleeding risk is pathophysiologically plausible, but this cannot be answered by our current data. In addition, women and men differed in RV hemodynamics. In line with prior studies,[6,7] we showed that women had a higher incidence of perioperative RV failure requiring more additional RV support, although no difference in preoperative RV function was seen. With respect to the observed higher incidence of arrhythmias in women, RV failure may partly be explained by the occurrence of arrhythmias. In particular, ventricular arrhythmias have the potential to induce RV failure under LVAD support.[17]



Abbreviations: LVAD: left ventricular assist device, RVAD: right ventricular assist device.

Probabilities of death:

	% at 1 year after surgery	% at 2 years after surgery
LVAD men	16.8	26.8
LVAD women	24.5	34.1
LVAD, RVAD men	38.2	47.0
LVAD, RVAD women	38.3	58.8

Figure 2 Kaplan-Meier survival curves by gender and assist types (with mortality as endpoint). Patients who died or were censored in the first 30 days after surgery were excluded from analysis. Follow-up was censored at transplantation or recovery. Results of log-rank test (men vs women): LVAD, $p = 0.046$; LVAD, temporary RVAD, $p = 0.50$. Numbers at risk are given below the Kaplan-Meier curves. Patients with RVAD, BIVAD, total artificial heart, CircuLite Synergy, HeartWare MVAD, and not-specified device brands were excluded from analysis.

A possible relationship of device type and specific adverse events has to be considered. The HeartWare HVAD, which was significantly more often implanted in women, has been related to a higher rate of cerebrovascular events.[18] The centrifugal flow of the HeartWare HVAD pump was associated with a hypercoagulable state,[19] which renders thromboembolic events more plausible. Prior investigations showed that anticoagulation, antiplatelet therapy, and blood pressure management affected stroke rate after HeartWare HVAD implantation.[20] In our study, after adjustment for LVAD brands, the association of cerebral bleeding, ischemic stroke, and pump thrombosis with mortality did not change markedly. Therefore, the association of these adverse events with mortality cannot be explained by the device choice.

Survival and predictors for mortality

There is conflicting evidence for survival differences between genders undergoing VAD therapy across heterogeneous studies with mostly smaller numbers of participants and different device types. In studies performed with several device types, continuous-flow systems were shown to be related to better survival rates.[21] Morgan et al[4] found a significantly worse survival for women undergoing pulsatile-flow support. In contrast to other studies, which did not see differences in short-term survival,[6,7,9,13] women had a significantly worse 1- to 3-year survival in our study population. Our data provide evidence for 3 possible reasons for our findings. First, women were shown to present to the hospital in more advanced HF states.[4] Second, women suffered significantly more often from perioperative RV failure. Third, women are more likely to experience arrhythmias and major bleeding complications. In line with Shah et al,[22] we showed that need for percutaneous mechanical support was associated with perioperative mortality in both, women and men. INTERMACS profiles 1 and 2, which represent a clinically unstable condition, were identified to predict survival. We directly linked RV hemodynamics with mortality in both genders. In women with need for LVAD and temporary RVAD support, the probability of death was 38% at 1 year compared with 25% for women undergoing isolated LVAD support. This means that once temporary RVAD support is needed, the survival is significantly worse. However, as soon as women undergo additional RV support, no differences in outcome are seen compared to men with biventricular support. Whether a better preoperative evaluation of the right ventricle and a stricter determination of indication would improve the outcome on mechanical circulatory support needs to be further investigated.

In addition, the significant association of pump thrombosis with mortality was stronger in women. Prior studies showed that women experience thromboembolic events more often under VAD support and therefore may need more intensive anticoagulation.[9,23] Prospective studies are needed to verify if gender-specific anticoagulation regimens would reduce thromboembolic complications and improve survival of women on long-term assist device support.

Limitations

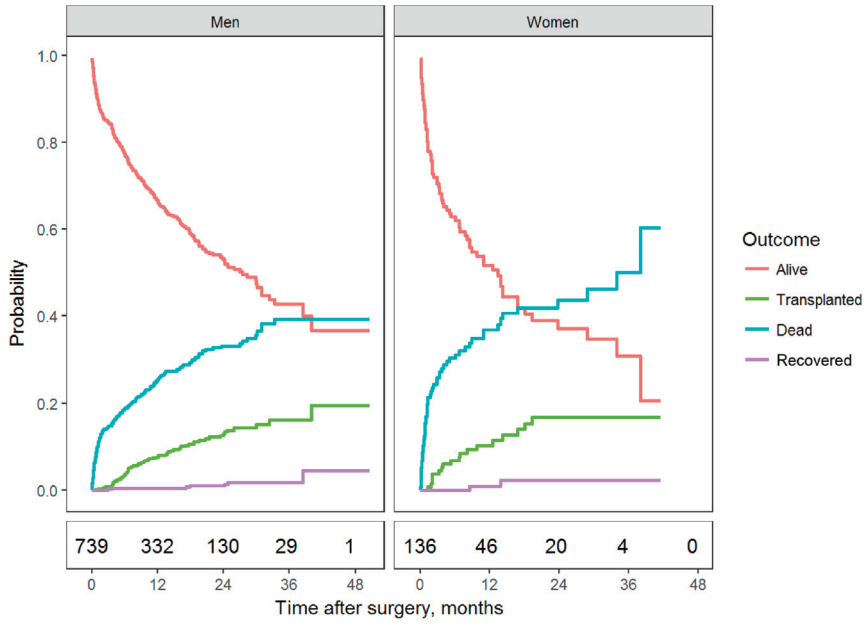
Data quality of a large registry relies on the data input of the participating centers. Therefore, the possibility exists that not all adverse events were reported. Furthermore, the very nature of a registry allows no analyses on center-specific trends and device choices.

Conclusions

In conclusion, we were able to demonstrate in a large European sample that women and men undergoing VAD support differ in preoperative condition, perioperative hemodynamics, adverse events, and survival. Women were shown to have a higher incidence of major bleeding, arrhythmias, and perioperative RV failure and a worse early and long-term survival. Several hemodynamic parameters and adverse events predicted survival in both, women and men. The association of pump thrombosis with mortality was stronger in women. Whether changes in referral strategies, implant timing, and gender-specific outpatient aftercare may improve outcome for women on VAD support needs to be investigated.

Disclosure statement

H.R. is a consultant for HeartWare. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.



Competing risk analyses

	% at 1 year Men	% at 2 years Men	% at 1 year Women	% at 2 years Women
Alive	66.6	53.3	51.8	37.2
Transplanted	7.6	12.6	10.3	16.8
Dead	25.4	33.1	36.9	43.8
Recovered	0.4	1.0	1.0	2.2

Figure 3 Cumulative incidence functions for both, women and men with the outcomes transplantation, death, and recovery. The probability of being alive without transplantation or recovery is also shown. Results of Gray's-Test (men vs. women): transplanted: $p = 0.33$; dead: $p = 0.004$; recovered: $p = 0.81$. Numbers at risk are shown below the curves. Patients with RVAD, BIVAD, total artificial heart, CircuLite Synergy, HeartWare MVAD, and not-specified device brands were excluded from analysis.

Table 4 Cox Regression Analyses for Selected Hemodynamic Parameters and Mortality With Interaction by Gender

Model	Gender	Hazard ratio (95% CI)	*p*-value	*N* events/ *N* individuals	*p*-value interaction
(1) Currently on intravenous inotropes					0.61
	Men	10.90 (7.59, 15.66)	<0.001	161/617	
	Women	13.19 (6.91, 25.19)	<0.001	39/108	
(2) Percutaneous mechanical circulatory support (IABP or ECMO)					0.034[a]
	Men	1.31 (0.93, 1.86)	0.13	204/723	
	Women	2.70 (1.54, 4.73)	<0.001	56/135	
(3) INTERMACS profile unstable condition					0.52
	Men	1.88 (1.42, 2.49)	<0.001	205/727	
	Women	2.29 (1.31, 4.01)	0.0036	54/134	
(4) Preoperatively highly reduced RV function[b]					0.5
	Men	2.69 (1.64, 4.44)	<0.001	176/613	
	Women	6.84 (2.14, 21.84)	0.0012	43/107	

All models are adjusted for age and LVAD brand. Patients receiving RVAD, BIVAD, total artificial heart, CircuLite Synergy, HeartWare MVAD, or not-specified device brands were excluded. Numbers vary slightly due to missing value information.

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RV, right ventricular.

[a]statistically significant.

[b]Hazard ratios for mildly and moderately reduced RV function are not shown.

Table 5 Cox Regression Analyses for Selected Adverse Events and Mortality With Interaction by Gender

Model	Gender	Hazard ratio (95% CI)	*p*-value	*N* deaths/ *N* individuals	*p*-value interaction
(1) Major bleeding					0.49
	Men	5.70 (4.14, 7.84)	<0.001	208/738	
	Women	4.55 (2.60, 7.95)	<0.001	56/136	
(2) Cerebral bleeding					0.22
	Men	12.06 (7.12, 20.42)	<0.001	208/738	
	Women	27.1 (8.95, 82.02)	<0.001	56/135	
(3) Ischemic stroke					0.86
	Men	3.65 (2.27, 5.84)	<0.001	208/739	
	Women	3.29 (1.18, 9.18)	0.023	56/136	
(4) Pump thrombosis					0.028[a]
	Men	3.27 (2.07, 5.16)	<0.001	208/737	
	Women	10.01 (4.44, 22.55)	<0.001	56/136	
(5) RV failure					0.36
	Men	8.39 (5.06, 13.91)	<0.001	208/739	
	Women	5.61 (2.77, 11.35)	<0.001	56/136	
(6) Renal dysfunction					0.023[a]
	Men	3.03 (1.71, 5.36)	<0.001	208/739	
	Women	0.67 (0.16, 2.74)	0.57	56/136	

All models are adjusted for age and LVAD brand. Patients receiving RVAD, BIVAD, total artificial heart, CircuLite Synergy, HeartWare MVAD, or not-specified device brands were excluded. Numbers vary slightly due to missing value information.
CI, confidence interval; RV, right ventricular.
[a]statistically significant.

EUROMACS is a committee of the European Association of Cardiothoracic Surgery (EACTS). Its foundation was financially supported by "Friede Springer Herzstiftung."

We thank Roland Hetzer and Jan Gummert and the 15 other founding international members for their initiative in implementing EUROMACS in 2009. We additionally thank Theo M.M.H. de By for running the registry and all participating European and non-European centers for providing their data of device implantation and long-term follow-up, which made our analyses possible.

Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org.

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