Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices

The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score

Editorial, see p XXX

BACKGROUND: The aim of the study was to derive and validate a novel risk score for early right-sided heart failure (RHF) after left ventricular assist device implantation.

METHODS: The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) was used to identify adult patients undergoing continuous-flow left ventricular assist device implantation with mainstream devices. Eligible patients (n=2988) were randomly divided into derivation (n=2000) and validation (n=988) cohorts. The primary outcome was early (<30 days) severe postoperative RHF, defined as receiving short- or long-term right-sided circulatory support, continuous inotropic support for ≥14 days, or nitric oxide ventilation for ≥48 hours. The secondary outcome was all-cause mortality and length of stay in the intensive care unit. Covariates found to be associated with RHF (exploratory univariate P<0.10) were entered into a multivariable logistic regression model. A risk score was then generated using the relative magnitude of the exponential regression model coefficients of independent predictors at the last step after checking for collinearity, likelihood ratio test, c index, and clinical weight at each step.

RESULTS: A 9.5-point risk score incorporating 5 variables (Interagency Registry for Mechanically Assisted Circulatory Support class, use of multiple inotropes, severe right ventricular dysfunction on echocardiography, ratio of right atrial/pulmonary capillary wedge pressure, hemoglobin) was created. The mean scores in the derivation and validation cohorts were 2.7±1.9 and 2.6±2.0, respectively (P=0.32). RHF in the derivation cohort occurred in 433 patients (21.7%) after left ventricular assist device implantation and was associated with a lower 1-year (53% versus 71%; P<0.001) and 2-year (45% versus 58%; P<0.001) survival compared with patients without RHF. RHF risk ranged from 11% (low risk score 0–2) to 43.1% (high risk score >4; P<0.0001). Median intensive care unit stay was 7 days (interquartile range, 4–15 days) versus 24 days (interquartile range, 14–38 days) in patients without versus with RHF, respectively (P<0.001). The c index of the composite score was 0.70 in the derivation and 0.67 in the validation cohort. The EUROMACS-RHF risk score outperformed (P<0.0001) previously published scores and known individual echocardiographic and hemodynamic markers of RHF.

CONCLUSIONS: This novel EUROMACS-RHF risk score outperformed currently known risk scores and clinical predictors of early postoperative RHF. This novel score may be useful for tailored risk-based clinical assessment and management of patients with advanced HF evaluated for ventricular assist device therapy.

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Clinical Perspective

What Is New?

- This project provides a novel and simple risk score for right-sided heart failure in adults undergoing left ventricular assist device implantation with current mainstream devices.
- Using 2988 adults (age >18 years) who underwent continuous-flow left ventricular assist device implantation across the European Union in the largest EU Registry of mechanical circulatory support devices, we derived and validated a right-sided heart failure prediction model that outperformed several published scores and well-known hemodynamic and echocardiographic individual markers of right-sided heart failure.
- The right-sided heart failure prediction model included the following risk factors: need of ≥3 inotropic agents, Interagency Registry for Mechanically Assisted Circulatory Support class 1 through 3, severe right ventricular dysfunction on semiquantitative echocardiography, ratio of right atrial to pulmonary capillary wedge pressure >0.54, and hemoglobin ≤10 g/dL.

What Are the Clinical Implications?

- Our findings offer a step toward improving prediction of the risk of right-sided heart failure among patients undergoing left ventricular assist device implantation.
- This score may help to target future optimal strategies aiming at early and intensive right-sided heart failure management for the highest-risk subgroups of the left ventricular assist device population.
- Future studies should determine whether early right ventricular assist device implantation or intensive right-sided heart failure medication can improve survival and reduce intensive care unit stay among left ventricular assist device candidates at high risk for right-sided heart failure.

Continuous-flow left ventricular (LV) assist devices (LVADs) are increasingly used in patients with end-stage heart failure (HF) as a bridge to transplantation, a bridge to candidacy, or destination therapy (DT). The 1-year survival reported for patients treated with continuous-flow LVAD was ≈80% and 73% in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), respectively.[1,2] Early post-LVAD mortality is due partly to the development of right-sided HF (RHF) in the early post-LVAD phase.[3] The pathophysiology of RHF, however, is not well known.[4,5] Post-LVAD RHF has been reported to be between 4% and 50%,[6–10] and RHF-associated 6-month mortality was seen in up to 29% of patients receiving an LVAD.[11] Moreover, RHF has a greater impact in patients who receive LVAD as DT, for whom there is no opportunity for bailout with heart transplantation.

Management of RHF depends primarily on the timing and severity of the condition. Patients with severe preoperative RHF are usually considered for biventricular support. In primary LVAD operations, post-LVAD patients with RHF often require prolonged inotropic support, nitric oxide (NO) ventilation, prolonged intensive care unit (ICU) stay, or temporarily a right ventricular (RV) assist device.

Prediction and early recognition of RHF could help in timely intervention and thus improvement of patients' outcome. Several prediction scores of RHF in patients with LVAD have been proposed.[9,11–13] Those prediction scores have mostly been based on earlier-generation LVADs and were derived from rather small populations or heterogeneous LVADs.

The objective of this study was to develop and validate a new simple score to predict early post-LVAD RHF in a large population with continuous-flow LVADs from the EUROMACS Registry.

METHODS

The EUROMACS Registry

The EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery. The registry gathers data for scientific analyses, aimed at improving care of patients with end-stage HF who require mechanical circulatory support.[2] All relevant clinical, echocardiographic, hemodynamic, and laboratory parameters were prospectively collected by participating sites in the EUROMACS Registry and entered into an electronic database (see Appendix I in the online-only Data Supplement for the list of the EUROMACS sites and investigators [alphabetic according to country]). The EUROMACS Registry began officially in January 1, 2011, but sites were also allowed to collect data retrospectively from patients who were already implanted before that date. A protocol for data collection and data entry, including all relevant data for the registry, was provided to all participating centers before data entry was allowed. Details of the registry and data collection are described elsewhere.[2] This study was approved by the institutional review committee of all respective participating centers, and all subjects gave informed consent.

Study Design

The present study was approved by the EUROMACS Committee. All patients (n=3897) undergoing LVAD implantation between January 2006 and May 2017 were identified. We excluded patients <18 years of age (n=171) and patients with primary devices (total artificial heart, single-ventricle assist device) other than LVAD (n=97). Devices other than mainstream (n=641) were also excluded (Figure 1).

Study Outcome

The primary outcome was early (<30 days) severe postoperative RHF, defined as receiving short- or long-term right-sided

circulatory support, continuous inotropic support for ≥14 days, or NO ventilation for ≥48 hours.[14] The secondary outcome was all-cause mortality and length of stay in the ICU. We used a hierarchy selection of the components of RHF definition in which the need for RV assist device has the strongest weight, the prolonged use of inotropes comes next, and the use of inhaled NO comes last. Of note, only a small minority were defined on the basis of the last outcome component.

Potential Predictors of RHF

We examined 82 potential preoperative predictors and cardiopulmonary bypass (CPB) time for the association with RHF. Preoperative clinical data included age, sex, body surface area, body mass index, ethnic origin and blood group type, HF etiology, New York Heart Association functional class, and INTERMACS class.[15] Comorbidity factors included diabetes mellitus, history of neurological events, carotid artery disease, history of cardiac arrest, use of mechanical ventilation, use of feeding tube, implantable cardioverter-defibrillator, history of major myocardial infarction, previous cardiac surgery, renal dialysis, ultrafiltration, and positive blood culture. Furthermore, LVAD strategies such as DT, use of an intra-aortic balloon pump, and use of extracorporeal membrane oxygenator were also included.

The preoperative use of HF medication included individual medications such as milrinone, dobutamine, dopamine, levosimendan, vasopressors, norepinephrine, and epinephrine, as well as the use of ≥3 intravenous inotropes. Amiodarone, angiotensin-converting enzyme inhibitors, β-blockers, aldosterone antagonists, loop diuretics, and anticoagulants were also examined.

Preoperative echocardiographic parameters were recorded and analyzed in accordance with published guidelines,[16,17] including tricuspid annular plane systolic excursion, RV dysfunction on visual score, LV diastolic and systolic dimensions and volumes, LV ejection fraction, and mitral, aortic, and tricuspid valvular regurgitation. Median duration of echocardiographic data collection before LVAD surgery was 6 days. Severity of valvular regurgitation was graded as none, trivial, mild, moderate, or severe according to published guidelines.[18,19]

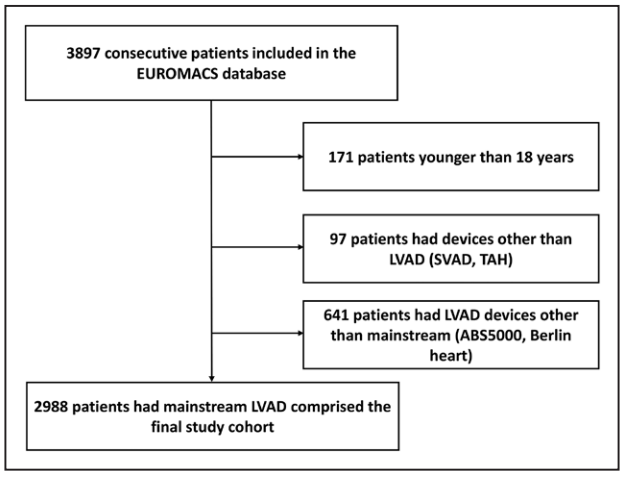

Figure 1. Flowchart of the study population.
EUROMACS indicates European Registry for Patients With Mechanical Circulatory Support; LVAD, left ventricular assist device; SVAD, single-ventricle assist device; and TAH, total artificial heart.

Hemodynamic predictors included cardiac rhythm, heart rate, systolic and diastolic blood pressures, and Swan-Ganz recordings. The Swan-Ganz recordings included systolic, diastolic, and mean pulmonary artery (PA) pressure; right atrial (RA) pressure; transpulmonary gradient; pulmonary vascular resistance; pulmonary capillary wedge pressure (PCWP); pulmonary and systemic vascular resistance; stroke index; and cardiac index. The transpulmonary gradient was calculated as the difference between the PA mean pressure and PCWP, which has a normal value of ≤12 mm Hg. Pulmonary vascular resistance is calculated as transpulmonary gradient divided by cardiac output, which has a normal value of <3 Wood units (or 240 dynes·s·cm^{-5}). The ratio of RA to PCWP and the PA pulsatility index[20] were also calculated. The RV systolic work index was calculated as follows: RV stroke volume index×(mean PA pressure−central venous pressure)×0.0136 expressed in grams per square meter per beat. The factor 0.0136 was used to covert pressure (millimeters of mercury) into work (grams per square meter). Normal values are 5 to 10 g/m^2 per beat.

Candidate laboratory variables included serum sodium and potassium levels; renal function parameters, including blood urea nitrogen; serum creatinine levels; and liver function parameters, including alanine transaminase, aspartate transaminase, lactate dehydrogenase, total bilirubin, and serum albumin levels. In addition, white blood count, platelets count, hemoglobin level, and serum C-reactive protein were evaluated.

Statistical Analysis

Patient characteristics are described as means (SD) or medians (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. Differences between patient groups were evaluated for continuous variables by the Student *t* tests (gaussian distribution) or nonparametric Mann-Whitney *U* tests (nongaussian distribution) and for categorical variables with the χ^2 test.

Univariate logistic regression analysis was applied to relate a broad range of preoperative parameters to the study outcome, including demographics, clinical values, comorbidities, medications, and echocardiographic, hemodynamic, and laboratory parameters. Variables with a value of $P<0.10$ entered the multivariate stage, and a logistic regression model was constructed to predict early post-LVAD RHF, applying the stepwise forward method, with a value of $P=0.05$ a model-entry criterion. All variables were checked for multicollinearity assumption using correlations, tolerance, and variable inflation factor to avoid redundancy in the prediction model. Casewise diagnostics were done, as well as a check for the Mahalonobis and Cook distances for outliers. Outliers outside 3 SD were omitted.

Dichotomization of all relevant continuous variables was performed at the 25th percentile (systolic blood pressure, diastolic blood pressure, cardiac index, PA pulsatility index, RV stroke work index, serum albumin, serum hemoglobin, and platelets), at the 50th percentile (body surface area, tricuspid annular plane systolic excursion, LV end-diastolic diameter, LV

Table 1. Baseline Characteristics of Patients Undergoing Left Ventricular Assist Device Implantation

Variables	Derivation Cohort (n=2000)	Validation Cohort (n=988)	*P* Value
Demographics			
Age, y	53±13	53±12	0.71
Female sex, n (%)	344 (17)	179 (18)	0.54
Body surface area, m^2	1.96±0.23	1.97±0.23	0.11
Body mass index, kg/m^2	26.0±5.1	26.3±4.9	0.18
White race, n (%)	1347 (67)	675 (68)	0.36
Nonischemic origin, n (%)	1335 (67)	650 (66)	0.60
Blood type O, n (%)	733 (37)	359 (36)	0.60
NYHA functional class, n (%)			0.93
III	635 (32)	299 (30)	
IV	805 (40)	404 (41)	
INTERMACS class, n (%)			0.57
1	222 (11)	111 (11)	
2	630 (32)	297 (30)	
3	513 (26)	263 (27)	
≥4	559 (28)	275 (28)	
IABP, n (%)	198 (10)	76 (8)	0.06
VA-ECMO, n (%)	178 (9)	95 (10)	0.52
Intravenous medication, n (%)			
Use of vasopressors	410 (21)	208 (21)	0.71
Use of ≥3 inotropes	239 (12)	119 (12)	0.93
Laboratory values			
Serum creatinine, mg/dL	1.20 (0.95–1.60)	1.20 (0.92–1.60)	0.69
AST, U/L	32 (22–63)	32 (22–77)	0.54
Total bilirubin, mg/dL	1.30 (0.82–2.09)	1.30 (0.79–2.10)	0.46
Albumin, g/dL	3.6 (3.0–4.2)	3.6 (2.9–4.2)	0.75
Hemoglobin, g/dL	12.2 (10.5–13.9)	11.7 (10.1–13.6)	0.78
Hemodynamic			
RA pressure, mm Hg	11 (7–15)	9 (6–15)	0.11
PCWP, mm Hg	25 (16–30)	22 (17–28)	0.91
PAPI	2.55 (1.50–3.75)	2.88 (1.65–4.25)	0.29
PAP, mean, mm Hg	35 (29–43)	34 (27–44)	0.58
RVSWI, g/m^2 per beat	6.7 (4.1–10.2)	6.8 (4.5–9.6)	0.91
RA/PCWP	0.48 (0.31–0.78)	0.42 (0.29–0.67)	0.12
Echocardiographic			
Severe RV dysfunction, n (%)	192 (10)	91 (9)	0.83
TAPSE, mm	14 (12–16)	15 (13–17)	0.59
Severe tricuspid regurgitation, n (%)	278 (14)	113 (11)	0.29
Severe mitral regurgitation, n (%)	218 (11)	134 (14)	0.97
LVEF grade <20%, n (%)	718 (36)	405 (41)	0.80

All continuous values are presented in mean±SD unless stated otherwise or presented as median (IQR).

AST indicates serum aspartate transaminase; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support (for INTERMACS classes, see text for details); LV, left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVSWI, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; and VA-ECMO, veno-arterial extracorporeal membrane oxygenator.

end-diastolic volume, systolic PA pressure, diastolic PA pressure, transpulmonary gradient, RA pressure, systemic vascular resistance, and RA/PCWP ratio), or at the 75th percentile (heart rate, CPB time, serum creatinine, serum alanine transaminase, serum aspartate transaminase, lactate dehydrogenase, total bilirubin, white cell count, and serum C-reactive protein). Dichotomization was based mainly on clinical relevance such as using the 25th percentile for a variable with a known association of its lower value and worse outcome and vice versa. In some cases such as the RA/PCWP ratio, we used the receiver-operating characteristic (ROC) curve area under the curve (AUC) analysis to calculate the best cutoff point for its association with RHF.

The relative magnitude of the model regression coefficients from statistically significant variables in the final multivariable model was used to calculate an individual patient's risk score for the development of post-LVAD RHF. The model discrimination abilities were evaluated by the c index of the final multivariate model. ROC curve analysis of the EUROMACS-RHF risk score was compared with published risk scores and with individual known markers of RHF. Finally, we validated the risk model in the validation cohort. The optimal cutoff value for the EUROMACS-RHF risk score was calculated through the ROC curve and the respective Youden index.

We handled the missing data by performing multiple imputations of all relevant parameters in the entire population. SPSS version 24 was used for multiple imputations using the automated function. After analyzing the patterns of missing values in the data set, we used the built-in automatic method that perform imputations based on data scanning. The automatic method scans the data and uses the monotone method if the data show a monotone pattern of missing values; otherwise, fully conditional specification is used. A 50% limit for the missing data was set to exclude variables with excessive missing data. No relevant parameter had >10% missing data. Furthermore, the vast majority of variables that were included in the final multivariable regression model had <5% missing data.

The incidence rate of post-LVAD RHF was calculated over the follow-up period. We plotted Kaplan-Meier curves for the occurrence of up to 2-year all-cause mortality according to the presence or absence of post-LVAD RHF and stratified by the EUROMACS-RHF risk score categories. The log-rank test was used to examine time to mortality differences in the Kaplan-Meier analyses. A 2-tailed value of $P<0.05$ was considered statistically significant, and all statistics were undertaken with SPSS statistics version 24 (IBM Corp, Armonk, NY) and the R-statistical package.

RESULTS

Patient Population

The final study population comprised 2988 patients with a mean age of 53±13 years and 523 women (18%). The majority were white (68%, n=2022). The main type of HF was nonischemic (66%, n=1985). The main indication for LVAD was bridge to candidacy (37%, n=1102), followed by bridge to transplantation (24.5%, n=731). HeartWare HVAD was the most used LVAD brand (50.5%, n=1509), followed by HeartMate II (40.3%, n=1204), and the minority received HeartMate 3 (8%, n=240).

Derivation and Validation Cohorts

The final study patients were randomly divided into derivation (67%, n=2000) and validation (33%, n=988) cohorts. Both cohorts were well matched in key baseline and operative characteristics (Tables 1 and 2). Mainstream device brands were HeartMate II (40% [n=800] versus 41% [n=404]), HeartMate 3 (9% [n=169] versus 7% [n=71]) (both manufactured by Thoratec Corp, now Abbott Laboratory, Pleasanton, CA), and HeartWare HVAD System (50% [n=1007] versus 51% [n=502])

Table 2. Operative Characteristics of Patients Undergoing Left Ventricular Assist Device Implantation

Operative characteristics	Derivation Cohort (n=2000)	Validation Cohort (n=988)	*P* Value
Main LVAD strategy, n (%)			0.20
BTT (on the list)	490 (25)	241 (24)	
BTC (possible BTT)	754 (38)	348 (35)	
DT	333 (17)	170 (17)	
LVAD device brand, n (%)			0.68
HeartMate II	800 (40)	404 (41)	
HeartMate 3	169 (9)	71 (7)	
Heart Ware HVAD	1007 (50)	502 (51)	
Surgical duration			
CPB time, min	85 (65–115)	85 (63–115)	0.89
Surgery time, min	212 (175–298)	220 (180–286)	0.55

BTC indicates bridge to candidacy; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; DT, destination therapy; and LVAD, left ventricular assist device.

(manufactured by HeartWare Corp, now Medtronic, Framingham, MA) in the derivation and validation cohorts, respectively (*P*=NS). The 3 main indications for LVAD were as bridge to transplantation (25% [n=490] versus 24% [n=241]), bridge to candidacy (38% [n=754] versus 35% [n=348]), and DT (17% [n=333] versus 17% [n=170]) in the derivation and validation cohorts, respectively (*P*=NS; Table 2).

Early Post-LVAD RHF

LVAD implantation was complicated by RHF in 433 patients (21.7%) in the early 30-day post-LVAD period. Diagnosis of RHF was based on the need for postoperative mechanical RV support in 141 patients (7.1%), the need for prolonged postoperative inotropic support in 327 (16.4%), and the need for prolonged NO ventilation in 17 (1%). Median time to RV assist device implantation was 1 day (IQR, 0–5 days). Components of RHF definition are shown on Figure I in the online-only Data Supplement.

Logistic Regression Analysis for Early Post-LVAD RHF

Exploratory univariate logistic regression analysis for early post-LVAD RHF yielded 58 potential covariates (*P*<10) of 83 tested variables, which are listed in Tables 3 and 4, as clinical, medication, laboratory, echocardiographic, hemodynamic, and operative covariates (Table 5). Covariates were eliminated because of reasons mentioned above such as collinearity, resulting in 21 variables in the multivariable model. Significant predictors of early post-LVAD RHF in the derivation cohort included INTERMACS class, need for multiple intravenous inotropes, severe RV dysfunction, RA/PCWP ratio, and hemoglobin. The final model has a c index of 0.70 in the derivation cohort.

Patients in INTERMACS class 1 through 3 had a 27% risk of RHF versus 12% risk for those in INTERMACS class 4 through 7 (*P*<0.001). Additionally, patients on ≥3 inotropic agents in the preoperative period had 42% risk of RHF versus 22% risk for those on ≤2 inotropic agents (*P*<0.001). In terms of semiquantitative echocardiographic assessment, patients with severe RV dysfunction on visual score had 50% risk of RHF versus 23% for those with better RV function. Furthermore, patients with an RA/PCWP ratio >0.54 had 27.1% risk of RHF versus 16.1% for those with lower ratio (*P*<0.001). Finally, patients with hemoglobin ≤10 g/dL had 35% risk of RHF versus 23% risk for those with hemoglobin >10 g/dL (*P*<0.001).

EUROMACS-RHF Risk Score

With the use of the relative magnitude of the coefficient of regression in the multivariable model in the

Table 3. Exploratory Unadjusted Univariable Analysis for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort

Covariate	Univariable Analysis OR (95% CI)	*P* Value
Demographic and clinical characteristics		
Age (per 1-y increase)	1.005 (0.996–1.013)	0.27
Female sex	1.032 (0.780–1.366)	0.83
Body surface area (per 1-m^2 unit increase)	1.501 (0.933–2.414)	0.09
Body mass index (per 1-kg/m^2 unit increase)	1.018 (0.997–1.039)	0.10
Race (white vs others)	3.785 (2.829- 5.064)	<0.001
Heart failure origin (nonischemic vs ischemic)	0.986 (0.787–1.236)	0.91
NYHA functional class (IV vs III)	1.677 (1.354–2.078)	<0.001
INTERMACS (1–3 vs 4–7)	2.969 (2.218–3.974)	<0.001
Blood type O (yes vs no)	1.153 (0.926–1.435)	0.20
Diabetes mellitus (yes vs no)	1.142 (0.505–3.055)	0.64
History of CVA (yes vs no)	0.966 (0.665–1.404)	0.86
Symptomatic PVD (yes vs no)	1.173 (0.742–1.856)	0.50
History of cardiac arrest (yes vs no)	2.240 (1.494–3.357)	<0.001
Use of mechanical ventilation (yes vs no)	2.457 (1.803–3.348)	<0.001
Use of feeding tube (yes vs no)	3.485 (2.382–5.099)	<0.001
ICD implantation (yes vs no)	1.054 (0.848–1.310)	0.63
COPD (yes vs no)	0.757 (0.529–1.083)	0.13
Prior major MI (yes vs no)	1.536 (1.536- 2.076)	0.005
Prior cardiac surgery (yes vs no)	1.501 (1.102- 2.045)	0.01
Renal replacement therapy (yes vs no)	4.191 (2.427–7.237)	<0.001
Ultrafiltration (yes vs no)	2.332 (1.497–3.635)	<0.001
Intra-aortic balloon pump (yes vs no)	1.983 (1.450–2.712)	<0.001
VA-ECMO (yes vs no)	3.565 (2.596–4.896)	<0.001
Medication use		
Use of vasopressors	3.026 (2.373–3.858)	<0.001
≥3 Intravenous inotropes	2.601 (1.953–3.466)	<0.001
Amiodarone	1.787 (1.415–2.257)	<0.001
ACE inhibitors	0.772 (0.611–0.975)	0.03
β-Blockers	0.521 (0.410–0.662)	<0.001
Aldosterone antagonists	0.611 (0.477–0.783)	<0.001
Loop diuretics	1.529 (1.067–2.193)	0.02
Anticoagulant therapy	3.040 (2.284–4.045)	<0.001

ACE indicates angiotensin-converting enzyme; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; PVD, peripheral vascular disease; and VA-ECMO, veno-arterial extracorporeal membrane oxygenator.

Table 4. Exploratory Unadjusted Univariable Analysis for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort Using Laboratory, Echocardiographic, and Hemodynamic Characteristics

Covariate	Univariable Analysis OR (95%CI)	*P* value
Laboratory characteristics		
Sodium	1.010 (1.002–1.018)	0.01
Potassium	1.237 (1.075–1.425)	0.003
BUN	1.004 (1.002–1.007)	0.001
Creatinine (per 1-unit increase)	1.407 (1.213–1.632)	<0.001
Creatinine >2.3 mg/dL (75%)	2.373 (1.662–3.389)	<0.001
AST >37 U/L	2.091 (1.661–2.633)	<0.001
ALT >72 IU/L	2.400 (1.736–3.319)	<0.001
LDH (>445 vs ≤445 U/L)	1.554 (1.173–2.058)	0.002
Total bilirubin >2 mg/dL	1.620 (1.260–2.082)	<0.001
Albumin (<3.3 vs ≥3.3 g/dL)	1.107 (0.809–1.515)	0.52
WBCs	1.050 (1.026–1.074)	<0.001
Hemoglobin ≤10 g/dL	1.628 (1.281–2.070)	<0.001
Platelets	0.996 (0.996–0.998)	<0.001
HCO_3 (per 1-mEq/dL increase)	0.996 (0.963–1.030)	0.80
Echocardiographic characteristics		
Severe RV dysfunction	3.535 (2.578–4.848)	<0.001
LV end-diastolic diameter (per 1-mm increase)	1.003 (1.000–1.006)	0.04
LV end-systolic diameter (per 1-mm increase)	1.004 (1.000–1.009)	0.05
LV end-diastolic volume (per 1-mL increase)	0.998 (0.995–1.001)	0.11
LV end-systolic volume (per 1-mL increase)	0.998 (0.994–1.002)	0.36
TAPSE (≤14 vs >14 mm)	1.241 (0.847–1.817)	0.27
LV ejection fraction (<20% vs >20%)	1.780 (1.391–2.278)	<0.001
Severe vs less severe mitral regurgitation	0.550 (0.389–0.777)	0.001
Severe vs less severe tricuspid regurgitation	0.917 (0.666–1.262)	0.59
Severe vs less severe aortic regurgitation	4.888 (1.483–16.114)	0.009
Hemodynamic characteristics		
Nonsinus vs sinus rhythm	1.202 (0.957–1.508)	0.11
Heart rate (≥96 vs <96 bpm)	1.445 (1.141–1.832)	0.002
Systolic blood pressure (≤85 vs >85 mm Hg)	1.623 (1.202–2.190)	0.002
Diastolic blood pressure (≤52 vs >52 mm Hg)	1.629 (1.199–2.213)	0.002
Cardiac index (≤1.2 vs >1.2 L/min)	0.817 (0.482–1.387)	0.46
PAP, systolic (≥53 vs <53 mm Hg)	1.220 (0.919–1.620)	0.17
PAP, diastolic (≥27 vs <27 mm Hg)	0.818 (0.617–1.085)	0.16
PAP, mean (≥35 vs <35 mm Hg)	0.967 (0.730–1.282)	0.82
RA pressure (≥11 vs <11 mm Hg)	1.729 (1.279–2.338)	0.001
PCWP (≥12 vs <12 mm Hg)	1.086 (0.649–1.819)	0.75
SVR (≥1488 vs <1488 mm Hg)	0.712 (0.479–1.059)	0.09
TPG (≥12 vs <12 mm Hg)	1.043 (0.758–1.436)	0.80
PVR (≥3.3 vs <3.3 mm Hg)	0.163 (0.027–0.983)	0.05
PAPI (≤1.6 vs >1.6)	2.175 (1.584–2.988)	<0.001
RVSWI (≤4.6 vs >4.6 g/m^2 per beat)	1.481 (1.051–2.086)	0.03
RA/PCWP (>0.54 vs ≤0.54)	2.075 (1.383–3.112)	<0.001

ALT indicates alanine transaminase; AST, serum aspartate transaminase; BUN, blood urea nitrogen; CI, confidence interval; HCO, bicarbonates; LDH, *lactate dehydrogenase;* LV, left ventricular; OR, odds ratio; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVSWI, right ventricular stroke work index; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; and WBC, white blood cell.

Table 5. Exploratory Unadjusted Univariable Analysis of Operative Characteristics for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort

Covariate	Univariable Analysis OR (95%CI)	*P* Value
LVAD strategy		
BTT vs other	0.441 (0.334–0.583)	<0.001
LVAD device brand		
HeartMate II	1 (Reference)	
HeartMate III	1.734 (1.364–2.204)	<0.001
HeartWare HVAD	1.803 (1.211–2.684)	0.004
Surgical duration		
CPB time (per 10-min increase)	1.041 (1.020–1.062)	<0.001
CPB time >100 min (yes vs no)	1.544 (1.235–1.929)	<0.001
Surgery time (per 10-min increase)	1.020 (1.010–1.030)	<0.001
Surgery time >215 min (yes vs no)	1.377 (1.098–1.726)	0.006

BTT indicates bridge to transplantation; CI, confidence interval; CPB, cardiopulmonary bypass; LVAD, left ventricular assist device; and OR, odds ratio. For manufacturers of the LVADs, see text.

derivation cohort, points were assigned to the 5 covariates (Table 6). Values were rounded to the nearest integer to simplify the calculation of the composite risk score in routine clinical practice. A total 9.5-point score was generated.

Predictive Power of the EUROMACS-RHF Risk Score in the Derivation Cohort

The mean score in the derivation cohort was 2.7±1.9, ranging from 0 to 9.5 (Figure 2A). Likewise, data on the operative EUROMACS-RHF risk score are shown in Figure 2B. The predicted rate of RHF was significantly (*P* for linear trend <0.001) increased from 11% for a score of 0 to 2 to 43.1% for a score of >4 (Figure 3A). Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score are presented in Table I in the online-only Data Supplement, and those of the operative EUROMACS-RHF risk score are presented in Table II in the online-only Data Supplement.

Validation of the EUROMACS-RHF Risk Sore

The mean score in the validation cohort was 2.6±2.0, ranging from 0 to 8.5 (Figure 2A). The predicted rate of RHF was similar and significantly (*P*<0.001 for linear trend) increased from 12.5% for a score of 0 to

Table 6. European Registry for Patients with Mechanical Circulatory Support Multivariable Model for Right-Sided Heart Failure Derived From the Derivation Cohort

Variables	OR	Lower 95% CI	Upper 95% CI	χ^2 Value (χ^2=56.9)	Coefficients	Score
Preoperative model						
RA/PCWP >0.54	2.075	1.383	3.112	12.441	0.730	2
Hemoglobin ≤10 g/dL	1.611	1.037	2.502	4.506	0.477	1
Multiple intravenous inotropes	3.197	1.851	5.524	17.355	1.162	2.5
INTERMACS class 1–3	2.903	1.723	4.893	16.014	1.066	2
Severe RV dysfunction*	2.055	1.183	3.57	6.534	0.720	2
Postoperative RHF model after adding CPB time						
RA/PCWP >0.54	2.151	1.412	3.278	12.699	0.766	1
Hemoglobin ≤10 g/dL	2.609	1.544	4.409	12.839	0.959	1.5
Multiple intravenous inotropes	3.013	1.712	5.302	14.635	1.103	2
INTERMACS Class 1–3	3.393	1.946	5.915	18.561	1.222	2
Severe RV dysfunction*	2.099	1.193	3.694	6.618	0.742	1
CPB time >100 min	2.032	1.296	3.184	9.562	0.709	1

CI indicates confidence interval; CPB, cardiopulmonary bypass; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; OR, odds ratio; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RHF, right-sided heart failure; and RV, right ventricular.

See Appendix I in the online-only Data Supplement for an explanation of how to use this table to predict an individual patient's risk of RHF.

Examples of risk score calculation using the model presented in Table 6.

The following example illustrates the use of Table 6 to calculate the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) RHF risk score of early postoperative RHF after LVAD implantation in individual patients:

Consider a patient who was referred to left ventricular assist device implantation who has INTERMACS class 3, has severe RV dysfunction on echocardiography, has an RA/PCWP ratio of 0.55 on Swan-Ganz catheter, is on 3 inotropic support, and has a hemoglobin of 10 g/dL. Using the EUROMACS-RHF risk score of RHF model coefficients in Table 6, this patient's preoperative risk score for RHF is the highest because he scored all points (2+1+2.5+2+2=9.5) according to the prediction model. Furthermore, if this patient had CPB time >100 min, this patient's postoperative risk score for RHF with a similar formula will be 8.5 points.

*Semiquantitative assessment of RV systolic function on echocardiography.

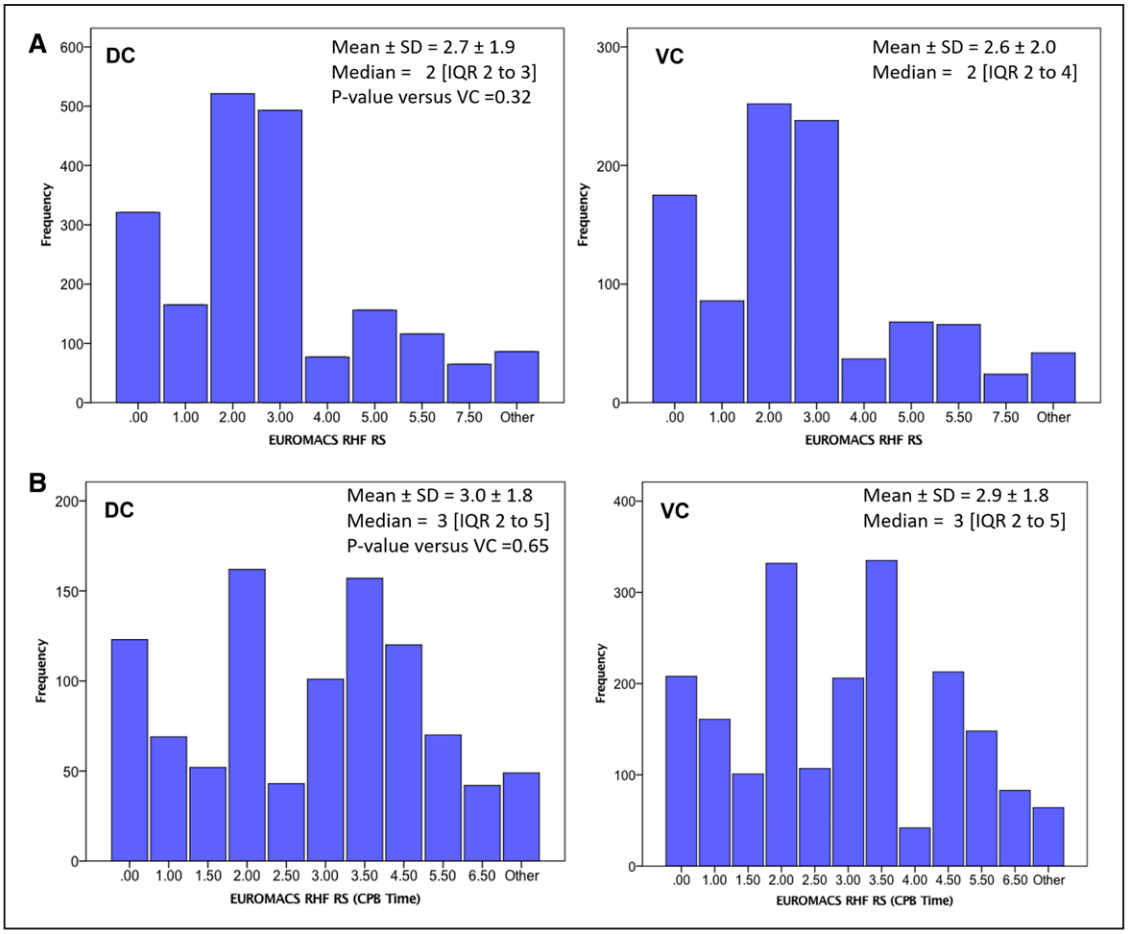

Figure 2. Distribution of the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) right-sided heart failure (RHF) risk score (A) and the postoperative EUROMACS-RHF risk score (B) in the derivation cohort (DC) and the validation cohort (VC).

CPB indicates cardiopulmonary bypass; IQR, interquartile range; and RS, risk score.

2 to a 42.4% for a score of >4 (Figure 3B). The c index was 0.70 in the derivation versus 0.67 in the validation cohort (Figure II in the online-only Data Supplement). The Hosmer-Lemeshow goodness-of-fit *P* value was 0.61 in the validation cohort, which reflects an appropriate fit for the data in this cohort. A comparison of the ROC curve of the EUROMACS-RHF risk score with a modified score that includes CPB time >100 minutes and 2 previously published RHF scores derived from continuous-flow LVAD populations demonstrated higher AUC for the EUROMACS-RHF risk score compared with the Kormos et al[11] (*P*<0.001) score and the Central Venous Pressure >15 mmHg, Severe RV Dysfunction, Preoperative Intubation, Severe Tricuspid Tegurgitation, Tachycardia[21] (*P*<0.001) score (Table 7). AUC was similar for the EUROMACS-RHF and modified postoperative EUROMACS-RHF scores (*P*=0.41). ROC curve comparison with other individual known hemodynamic and echocardiographic markers of RV failure demonstrated the highest AUC for the EUROMACS-RHF score (all *P*<0.001).

EUROMACS-RHF Risk Score and All-Cause Mortality

Cumulative survival in the postoperative 24 months was higher in patients without RHF at the 6-month (79% versus 61%), 12-month (71% versus 53%), 18-month (65% versus 49%), and 24-month (58% versus 45%) follow-up compared with patients with RHF (log-rank test, *P*<0.001; Figure 4A). Likewise, cumulative survival in the postoperative 24 months was at the 6-month (80% versus 66% versus 56%), 12-month (73% versus 60% versus 48%), 18-month (66% versus 54% versus 46%), and 24-month (61% versus 46% versus 43%) follow-up patients with low, intermediate, and high EUROMACS-RHF risk score, respectively (log-rank test, *P*<0.001; Figure 4B). Multiorgan failure and sepsis were the most frequent primary causes of death, in particular in patients with RHF. Other common causes of death were cerebrovascular accidents, bleeding, and cardiopulmonary failure (Figure 5). Multiorgan failure was seen in 50% of patients who died with sepsis as the primary cause of death.

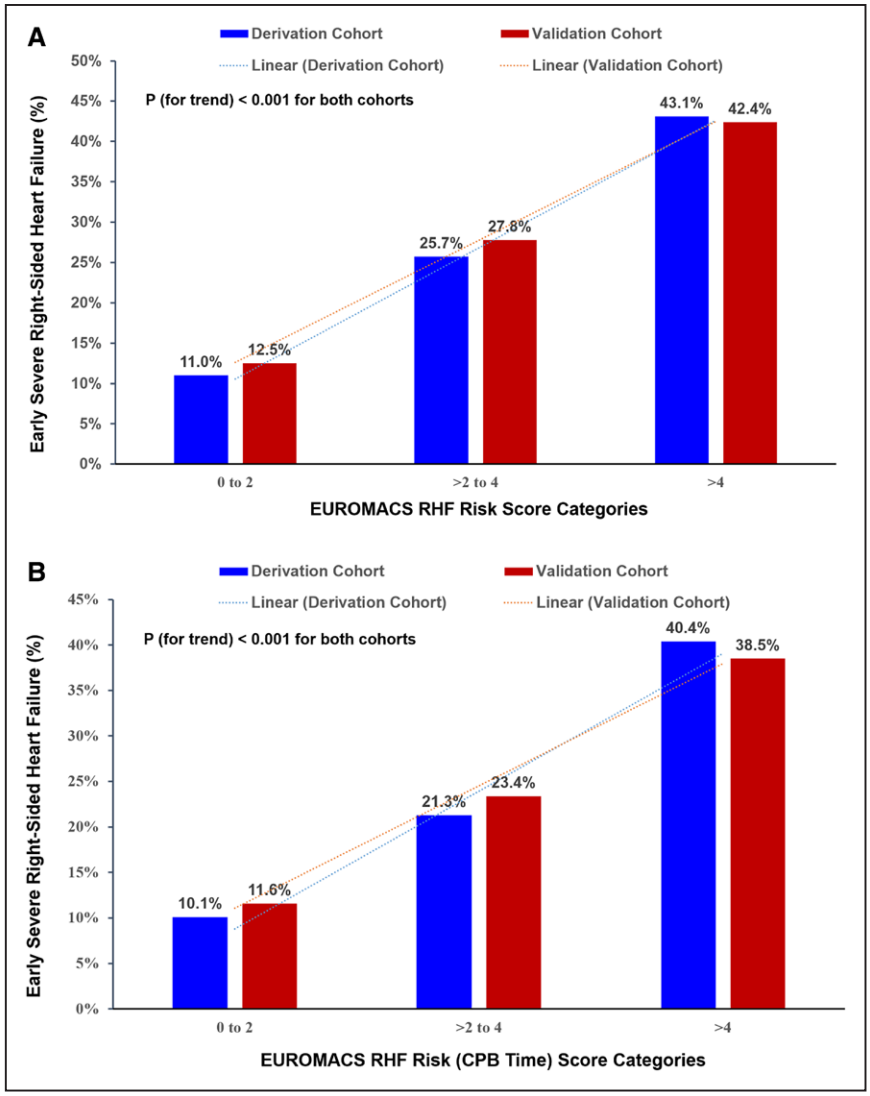

Figure 3. Frequency of early right-sided heart failure (RHF) stratified by (A) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score and (B) the postoperative EUROMACS-RHF risk score categories.
CPB indicates cardiopulmonary bypass.

EUROMACS-RHF Risk Score and ICU Stay Duration

Median ICU stay was 7 days (IQR, 4–15 days) versus 24 days (IQR, 14–38 days) in patients without versus with RHF (P<0.001). Likewise, the ICU stay was linearly increased from 6 days (IQR, 4–13 days) versus 13 days (IQR, 6–25 days) versus 19 days (IQR, 9–31 days) in the EUROMACS-RHF score low, intermediate, and high risk category, respectively (P<0.001 for trend; Figure 6A and 6B).

Subgroup Analysis

We performed subgroup analysis to test the predictive value of the EUROMACS-RHF risk score in patient populations treated with different LVADs. The incidence of RHF was 15.5% versus 24.1% versus 24.9% for patients treated with HeartMate II, HeartWare, and HeartMate 3, respectively (P<0.001 for trend; Table III in the online-only Data Supplement). In the derivation cohort, the AUC of the EUROMACS-RHF risk score was 0.75, 0.66, and 0.60 in the HeartMate II, HeartWare, and HeartMate 3 populations, respectively (Table IV in the online-only Data Supplement). Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the device brand subgroups are presented on Tables V–VII in the online-only Data Supplement.

DISCUSSION

This study is a multicenter study that includes the largest European population of patients who received currently used continuous-flow LVADs, evaluating the risk for RHF. Early severe RHF occurs in one fifth of patients with LVAD in this study and is associated with high mortality, up to 29% in some series.[11] We developed and validated a novel EUROMACS-RHF risk score using a simple 5-item scoring system for the prediction of early RHF after continuous-flow LVAD implantation.

Table 7. Performance Characteristics of Clinical Risk Prediction Scores and Individual Predictors for Right-Sided Heart Failure in the Derivation Cohort

	C Index (95% CI)	*P* Value
Risk scores		
EUROMACS-RHF risk score*	0.70 (0.67–0.73)	1 (Reference)
Postoperative EUROMACS-RHF risk score†	0.71 (0.68–0.74)	0.41
Kormos et al[11] score	0.58 (0.54–0.61)	<0.0001
CRITT score[21]	0.63 (0.60–0.66)	<0.0001
Individual hemodynamic parameters		
RA pressure, mm Hg	0.60 (0.55–0.65)	<0.0001
TPG, mm Hg	0.55 (0.50–0.61)	<0.0001
PVR, woods unit	0.56 (0.51–0.61)	<0.0001
RVSWI, g/m^2 per beat	0.52 (0.47–0.56)	<0.0001
Severe RV dysfunction	0.57 (0.52–0.61)	<0.0001

CI indicates confidence interval; EUROMACS, European Registry for Patients with Mechanical Circulatory Support; CI, confidence interval; CRITT, Central Venous Pressure >15 mmHg, Severe RV Dysfunction, Preoperative Intubation, Severe Tricuspid Tegurgitation, Tachycardia; PVR, pulmonary vascular resistance; RA, right atrial; RHF, right-sided heart failure; RV, right ventricular; RVSWI, right ventricular stroke work index; and TPG, transpulmonary gradient.

**P* value is EUROMACS-RHF risk score versus other scores or individual parameters.

The preoperative score includes need of ≥3 inotropic agents, Interagency Registry for Mechanically Assisted Circulatory Support class 1 through 3, severe RV dysfunction on semiquantitative echocardiography, RA/pulmonary capillary wedge pressure ratio >0.54, and hemoglobin ≤10 g/dL.

†The modified postoperative score includes cardiopulmonary bypass time >100 minutes and the 5 preoperative components of the EUROMACS-RHF risk score.

RHF is an important and frequent complication in the early postoperative period after LVAD implantation.[3] In prior studies, rates of post-LVAD RHF have ranged between 4% and 50%.[6–10] This wide range of reported RHF incidence is due partly to the lack of a universal definition of post-LVAD RHF across the literature. In primary LVAD implantation, severe RHF requires either mechanical RV support via RV assist device or extracorporeal membrane oxygenator, pharmacological support via the use of continuous intravenous inotropic support, or pulmonary vasodilators such as inhaled NO. Those 3 components are used in the RHF definition in this study, which is in line with the INTERMACS definition of severe RHF.[14]

Risk stratification of patients undergoing LVAD implantation is important to identify candidates for RV support, to provide timely pharmacological intervention, and thus to improve patients' outcome. This could be important in the decision process, preoperative preparation, and timing of surgery. This should be reflected also in the informed consent of the patients and the family, especially in patients receiving DT in whom there is no opportunity for bailout with heart transplantation. Few risk-scoring systems have been described to predict post-LVAD RHF. However, those studies are limited by small sample size, single centers, and the heterogeneous nature of LVADs. Kormos et al[11] and Atluri et al[21] investigated multivariate predictors of RHF in 484 and 167 patients, respectively, who received continuous-flow LVAD. However, the studies included only HeartMate II devices, disregarding other currently used mainstream LVADs such as HeartWare or the new HeartMate 3. In our study, the EUROMACS-RHF risk score was derived from a population of 2000 patients treated with mainstream LVADs.

Risk Score Components

The EUROMACS-RHF risk score is composed of severe RV dysfunction (2 points), ratio of RA/PCWP ≥0.54 (2 points), advanced INTERMACS class 1 through 3 (2 points), need for ≥3 intravenous inotropes (2.5 points), and hemoglobin ≤10 g/dL (1 point).

Because of the multifactorial nature of RHF after LVAD,[4,5] 83 parameters of clinical relevance are examined in this study for possible association with early post-LVAD RHF.

Patients with preoperative severe RV dysfunction on echocardiography have an ≈2-fold increase in the incidence of evident RHF in the early post-LVAD period compared with those without severe RV dysfunction. Echocardiographic assessment of RV function is readily available to assess RV contractility at bedside. Of note, there is a potential high variability in visual scoring of RV function on a scale from normal to severe; therefore, a quantitative marker such as RV fractional area change or the recently introduced iRotate echocardiography[22] can accurately quantify RV function. Nevertheless, visual assessment of a severe RV dysfunction on echocardiography in daily practice is, in our expert opinion, simple but robust.

Likewise, an elevated RA pressure in relation to pulmonary capillary wedge pressure shows a similar association with clinically evident early post-LVAD RHF. On the one hand, high RA pressure is a sign of RV failure; on the other hand, it could be a sign of volume overload. Aggressive diuresis, usually with inotropic support, and sometimes ultrafiltration, in case of ineffective diuresis, should be tried in patients with volume overload to achieve optimal euvolemic state.

In the EUROMACS database, as well as in other published data, most patients who are receiving an LVAD have some degree of RV dysfunction. In this study, 88% of patients have mild or more impairment of RV systolic function. However, RV dysfunction could remain silent as a result of a limited RV preload. RV preload has to increase immediately after LVAD to match increased LVAD workload. Furthermore, LV unloading tends to cause a leftward shift of the interventricular septum, therefore compromising effective RV contractility and aggravating the already impaired RV systolic function. The interventricular septum contributes to at least one third of the RV contractility.[23] Therefore, it is important to optimize LVAD flow to prevent excessive LV suction to avoid a vicious circle of RV function impairment.

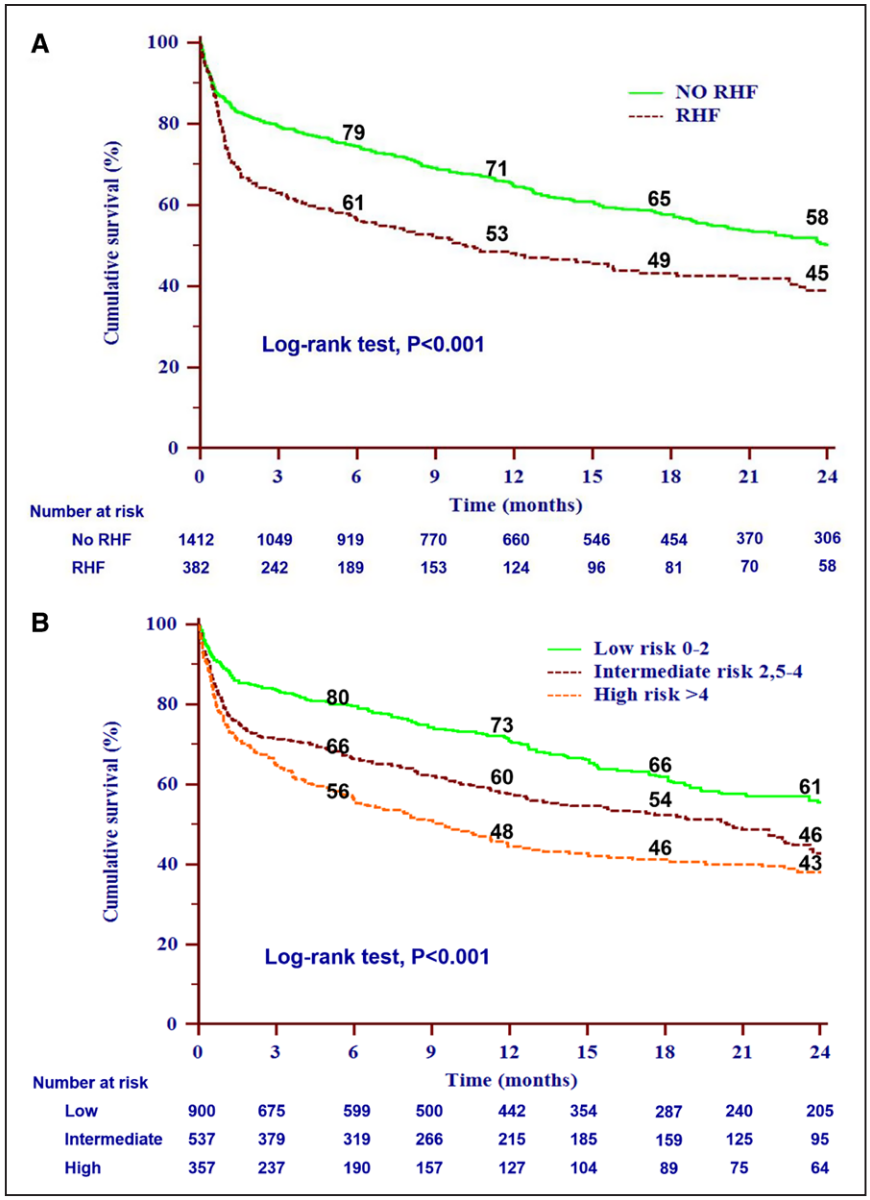

Figure 4. Two-year Kaplan-Meier estimates of death resulting from any cause stratified by (A) right-sided heart failure (RHF) and (B) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score strata.

The need for multiple inotropes in the preoperative period in this study was seen in 12% of patients and is associated with an ≈2-fold higher risk of RHF than in patients with ≤2 inotropes. The use of multiple inotropes has the greatest weight in predicting post-LVAD RHF among all 5 predictors. This might reflect, in fact, the biventricular origin of hemodynamic instability. Despite the dire need for inotropic support in those patients, excess or prolonged use of intravenous inotropic agents could have a detrimental effect on the myocardial energetics and metabolism.[24] In this study, an average of 1.5 inotropes were used per patient. Moreover, dobutamine was the most (53%) used inotropic agent (Figure III in the online-only Data Supplement). On the other hand, 12% of patients received levosimendan. Levosimendan is currently available in the European Union and various countries but remains investigational in the United States.[25] Levosimendan could prevents the development of RHF and improves contractility in established pressure overload–induced RV failure in the preclinical setting.[26] However, the short- and long-term outcomes of those inotropic agents have not been demonstrated in randomized clinical trials. Further studies are needed to test their role in early intensive management of RHF. As a potential example, a randomized study could be designed to test a temporary RV circulatory support in patients who are on or require >2 inotropes before LVAD implantation. In this proposed trial, patients could be randomized to an early temporary mechanical circulatory support or to escalating the number or doses of inotropic or vasopressor support.

An advanced INTERMACS score is found in this study to be associated with an ≈5-fold increase in the incidence of evident RHF in the early post-LVAD period compared with those with less advanced INTERMACS class before LVAD. This finding is in line with published data from the INTERMACS database.[27] We categorized patients according to

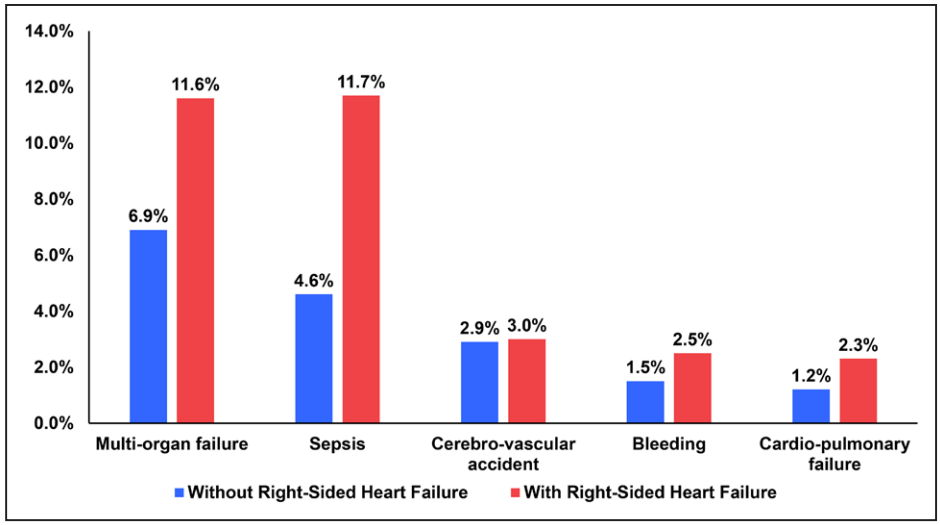

Figure 5. Five main known causes of death in the derivation cohort.

the modifiers of the INTERMACS profile definition into a group of hospitalized patients on intravenous inotropes or temporary circulatory support (class 1 through 3) and a second group including "frequent flyers" (class 4) and less sick (class 5 through 7) patients.[28] The first group represents sicker and decompensating patients who suffer severe hemodynamic derangement, threatening secondary organ (renal, hepatic) failure, compared with ambulatory, less sick, or relatively stable patients in the second group.

Finally, anemia as demonstrated with hemoglobin ≤10 g/dL was associated with 1.5-fold increase in post-LVAD RHF. Anemia is found in about one third of patients with chronic HF. The most common causes are chronic renal failure and iron deficiency. It could be speculated that anemia could play a role in triggering RHF in the setting of already vulnerable RV, and multiple blood transfusions in the early postoperative period could play a role in the pathophysiology of RHF in those patients. Blood transfusion–associated circulatory overload has been associated with an increased risk of RHF.[29,30] Furthermore, the already vulnerable RV is very likely to be challenged by borderline perfusion and thus impaired oxygen delivery resulting from anemia. On the other hand, anemia might reflect the severity of the underlying multiorgan failure. Impaired nutrition, malabsorption (resulting from congestion and abnormal production of hepcidin), and reduced intracellular uptake of iron have been reported as causes of anemia in patients with HF.[31,32]

In this study, we examined CPB time and LVAD surgery time in the prediction model of early post-LVAD RHF. Both parameters are significantly associated with the incidence of early post-LVAD RHF; however, a CPB time >100 minutes remained significant in the final model. It is associated with a 2-fold increase in the incidence of early post-LVAD RHF, but it did not improve much the AUC of the composite score.

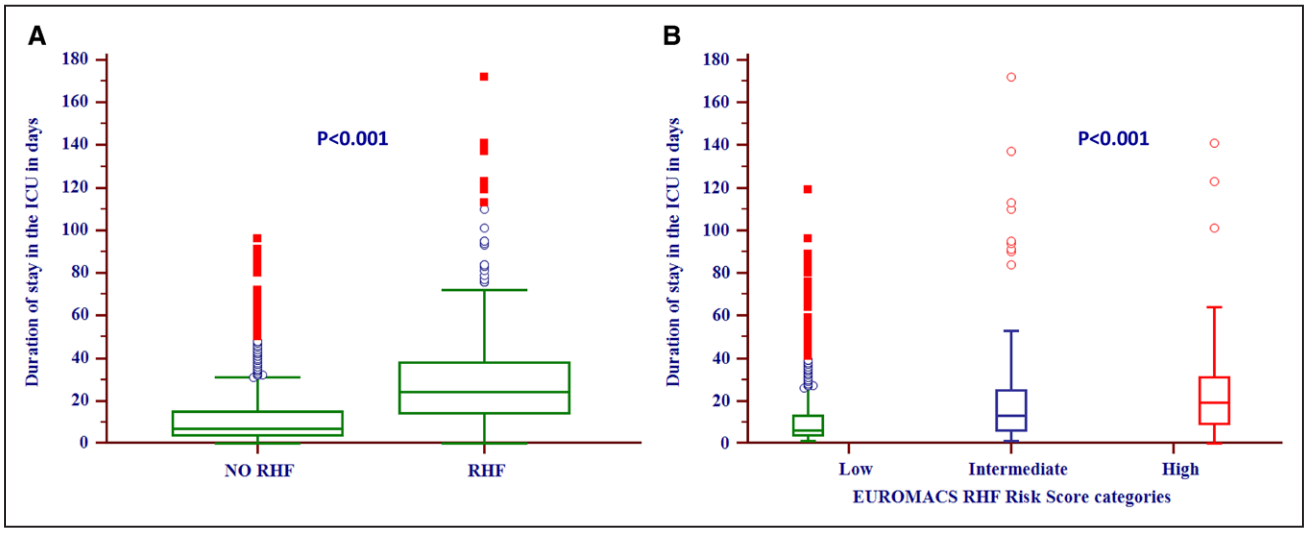

Figure 6. Median intensive care unit (ICU) stay in days stratified by (A) right-sided heart failure (RHF) and (B) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score strata.

Clinical Implications

In this study, RHF was associated with increased early and late mortality. Most common causes of death were multiorgan failure, sepsis and cerebrovascular accidents. Patients with RHF died more often as a result of multiorgan failure and sepsis. Those patients have severe systemic congestion and tissue hypoperfusion from underfilling of the LVAD. Moreover, patients with RHF had a longer ICU stay. It has been reported that ≈50% of ICU patients had a nosocomial infection and are therefore at a high risk for sepsis.[33] Furthermore, intestinal source of infection is a known source of sepsis in patients with multiorgan failure in the ICU as a result of translocation of gut flora into bloodstream.

In this study, the composite 5-point score predicts early post-LVAD RHF, with graded risk for both RHF and death seen with higher scores. The score is simple, validated, and composed of widely available and clinically relevant variables derived from a multivariate logistic regression analysis. In contrast, the more complex recently published machine prediction bayesian models[34] from the INTERMACS database consisted of 33 to 34 preoperative variables.

Our model variable selection was based on biological plausibility and knowledge of experts in the field to avoid redundancy in the model and unexplained or unexpected predictors. This risk score includes intuitive predictors that are known to be relevant in the pathophysiology of early post-LVAD RHF and its associated mortality. Furthermore, the final model of the EUROMACS-RHF risk score was validated in a separate validation cohort.

This novel scoring system may provide clinicians with opportunity for tailored risk decision making before, during, or early after LVAD surgery. A patient with a high risk score may require perioperative optimization of RV support, biventricular assist device, or total heart support. Optimization of RV support could be achieved via reduction of preload, afterload, and RV contractility support. Aggressive diuresis, early use of pulmonary vasodilators such as NO, phosphodiesterase type 5 inhibitors, or early RV mechanical support may be indicated. Furthermore, measures such as tricuspid valve repair could be considered. Those patients would benefit from early recognition in terms of not only less need for prolonged ICU stay but also, more important, better survival. However, those corrective measures remain speculative and should be tested in some prospective randomized trials to prove their usefulness.

Limitations

Caution should be taken in general against using solely a risk model for clinical decision making without prospective validation in randomized clinical trials. There are several limitations that should be acknowledged in this study. First, a validation ROC of 0.67 of this risk score is not ideal. It could be due to the fact that only very few patients were assigned to some high scores. The score could perform better in a larger population in which more patients are represented in all score levels. Another limitation is the semiquantitative assessment of RV function on echocardiography. A quantitative and preferably advanced RV assessment such strain analysis could improve the score performance. On the other hand, the widely used scores, also simple, such as $CHADS_2$-VASC[35] and even Pooled Cohort equations[36] are not different from this score. Furthermore, it may not be appropriate to generalize our findings to other types of VAD not included in the present analysis. However, the 3 LVADs in this study represent the mainstream LVADs used worldwide. An important limitation of this study is the retrospective analysis of the EUROMACS database. However, data on MCS devices are derived largely from registry databases. A prospective randomized study such as in patients with cardiogenic shock on multiple inotropes, which had the highest weight among RHF predictors, is warranted to prove the predictive value of this risk score.

Furthermore, there are potential confounders that might not be accounted for here. In addition, potential mechanisms of RHF that take place exclusively after LVAD surgery such as an immediate increase in RV work to match the increase in LVAD flow are not considered. Missing data were present for many of our variables. However, we addressed this issue by using multiple imputations, and no variables were missing in >90% of cases. Medication dosages were not considered in the present model. Pharmacological interventions could alter many biological markers such as hepatic and renal functional biomarkers, thus affecting the meaning of those markers in a prediction model. Of note, only hemoglobin appeared in the final step of the EUROMACS-RHF risk model.

Conclusions

We developed and validated the EUROMACS-RHF risk score, a simple 5-item scoring system for the prediction of early RHF and RHF-associated mortality after continuous-flow LVAD implantation. The score identified high-risk patients in whom timely optimization or mechanical RV support may be considered to reduce RHF-related mortality and morbidity.

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FOOTNOTES

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Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices:The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score

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SUPPLEMENTAL MATERIAL

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Derivation and Validation of a Novel Right Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: the EUROMACS-RHF Risk Score

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Supplemental Tables: I-VII

Supplemental Figures and Figure Legends: I-III

Appendix:

I. List of EUROMACS sites and investigators (alphabetical according to country)

Supplemental Tables

Supplementary Table I. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	99.2 - 100.0	0.00	0.0 - 0.2	1.00				21.6	19.9 - 23.5		
>0	92.84	90.0 - 95.1	18.51	16.6 - 20.5	1.14	1.0 - 1.3	0.39	0.3 - 0.5	23.9	21.9 - 26.1	90.3	86.6 - 93.3
>1	89.15	85.8 - 91.9	28.02	25.8 - 30.3	1.24	1.1 - 1.3	0.39	0.3 - 0.5	25.5	23.3 - 27.8	90.3	87.3 - 92.8
>2	74.36	70.0 - 78.4	57.18	54.7 - 59.6	1.74	1.6 - 1.9	0.45	0.4 - 0.5	32.4	29.5 - 35.4	89.0	86.9 - 90.8
>2.5 *	74.36	70.0 - 78.4	57.31	54.8 - 59.8	1.74	1.6 - 1.9	0.45	0.4 - 0.5	32.5	29.6 - 35.5	89.0	86.9 - 90.9
>3	46.88	42.1 - 51.7	81.17	79.1 - 83.1	2.49	2.2 - 2.8	0.65	0.6 - 0.7	40.8	36.4 - 45.2	84.7	82.8 - 86.5
>4	41.11	36.4 - 45.9	84.49	82.6 - 86.3	2.65	2.4 - 3.0	0.70	0.6 - 0.8	42.3	37.5 - 47.2	83.9	81.9 - 85.6
>4.5	38.34	33.7 - 43.1	86.02	84.2 - 87.7	2.74	2.4 - 3.1	0.72	0.6 - 0.8	43.1	38.1 - 48.2	83.5	81.6 - 85.2
>5	24.02	20.1 - 28.3	92.02	90.6 - 93.3	3.01	2.5 - 3.6	0.83	0.7 - 1.0	45.4	38.8 - 52.1	81.4	79.5 - 83.2
>5.5	13.63	10.5 - 17.2	96.55	95.5 - 97.4	3.95	3.1 - 5.0	0.89	0.7 - 1.2	52.2	42.6 - 61.7	80.2	78.3 - 82.0
>6	12.70	9.7 - 16.2	96.75	95.7 - 97.6	3.90	3.0 - 5.0	0.90	0.7 - 1.2	51.9	42.0 - 61.7	80.0	78.2 - 81.8
>6.5	11.09	8.3 - 14.4	97.06	96.1 - 97.8	3.78	2.9 - 4.9	0.92	0.7 - 1.2	51.1	40.5 - 61.5	79.8	77.9 - 81.6
>7	8.31	5.9 - 11.3	97.64	96.8 - 98.3	3.52	2.6 - 4.8	0.94	0.7 - 1.3	49.3	37.4 - 61.3	79.4	77.5 - 81.2
>7.5	0.92	0.3 - 2.3	99.74	99.3 - 99.9	3.62	1.4 - 9.6	0.99	0.4 - 2.6	50.0	13.9 - 86.1	78.5	76.6 - 80.3
>8.5	0.92	0.3 - 2.3	99.81	99.4 - 100.0	4.83	1.8 - 12.8	0.99	0.3 - 3.1	57.1	15.9 - 91.8	78.5	76.6 - 80.3
>9.5	0.00	0.0 - 0.8	100.00	99.8 - 100.0			1.00				78.3	76.5 - 80.1

Table II. The operative (CPB time) EUROMACS-RHF risk score

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	99.2 - 100.0	0.00	0.0 - 0.2	1.00				21.6	19.9 - 23.5		
>0	95.84	93.5 - 97.5	12.13	10.5 - 13.8	1.09	1.0 - 1.2	0.34	0.2 - 0.5	23.2	21.2 - 25.2	91.3	86.7 - 94.8
>1	91.45	88.4 - 93.9	21.19	19.2 - 23.3	1.16	1.1 - 1.3	0.40	0.3 - 0.5	24.3	22.2 - 26.4	90.0	86.4 - 92.8
>1.5	88.68	85.3 - 91.5	26.87	24.7 - 29.1	1.21	1.1 - 1.3	0.42	0.3 - 0.5	25.1	22.9 - 27.3	89.6	86.4 - 92.2
>2	81.29	77.3 - 84.9	46.01	43.5 - 48.5	1.51	1.4 - 1.6	0.41	0.3 - 0.5	29.4	26.8 - 32.1	89.9	87.6 - 91.9
>2.5	79.91	75.8 - 83.6	52.46	49.9 - 55.0	1.68	1.6 - 1.8	0.38	0.3 - 0.5	31.7	29.0 - 34.6	90.4	88.3 - 92.3
>3 *	70.21	65.7 - 74.5	62.92	60.5 - 65.3	1.89	1.8 - 2.0	0.47	0.4 - 0.6	34.4	31.2 - 37.6	88.4	86.4 - 90.2
>3.5	51.73	46.9 - 56.5	79.20	77.1 - 81.2	2.49	2.3 - 2.7	0.61	0.5 - 0.7	40.7	36.6 - 45.0	85.6	83.7 - 87.4
>4	47.34	42.6 - 52.2	80.66	78.6 - 82.6	2.45	2.2 - 2.7	0.65	0.6 - 0.7	40.4	36.1 - 44.8	84.7	82.8 - 86.5
>4.5	31.41	27.1 - 36.0	89.85	88.3 - 91.3	3.10	2.7 - 3.6	0.76	0.7 - 0.9	46.1	40.3 - 52.0	82.6	80.7 - 84.4
>5	28.87	24.6 - 33.4	90.75	89.2 - 92.1	3.12	2.7 - 3.6	0.78	0.7 - 0.9	46.3	40.2 - 52.4	82.2	80.3 - 84.0
>5.5	14.32	11.2 - 18.0	96.17	95.1 - 97.1	3.74	3.0 - 4.7	0.89	0.7 - 1.1	50.8	41.6 - 60.0	80.2	78.4 - 82.0
>6	13.86	10.7 - 17.5	96.23	95.2 - 97.1	3.68	2.9 - 4.7	0.90	0.7 - 1.2	50.4	41.1 - 59.7	80.2	78.3 - 82.0
>6.5	4.39	2.7 - 6.8	98.92	98.3 - 99.4	4.04	2.6 - 6.3	0.97	0.6 - 1.6	52.8	35.2 - 69.8	78.9	77.0 - 80.7
>7.5	0.00	0.0 - 0.8	99.94	99.6 - 100.0	0.00		1.00	0.1 - 7.1	0.0	0.0 - 97.5	78.3	76.5 - 80.1
>8.5	0.00	0.0 - 0.8	100.00	99.8 - 100.0			1.00				78.3	76.5 - 80.1

Supplementary Table III. Subgroup analysis (LVAD brand)

Incidence of right heart failure score stratified according to left ventricular assist device brand

			HeartMate II LVAS	HeartWare HVAD	Thoratec - HeartMate 3	
Derivation Cohort (n=2000)	Early Post-LVAD RHF	No	676 (84.5%)	764 (75.9%)	127 (75.1%)	1567 (79.3%)
		Yes	124 (15.5%)	243 (24.1%)	42 (24.9%)	433 (21.6%)
*Validation Cohort (n=988)	Early Post-LVAD RHF	No	340 (84.2%)	380 (75.7%)	45 (63.4%)	765 (78.3%)
		Yes	64 (15.8%)	122 (24.3%)	26 (36.6%)	212 (22.6%)

*Missing device type (n=24)

Supplementary Table IV. Performance characteristics of EUROMACS-RHF score for risk prediction of RHF stratified by brand of left ventricular assist device in the derivation cohort.

Cohort	Device Brand LVAD	Area	Std. Error[a]	p-value[b]	95% Confidence Interval	
					Lower Bound	Upper Bound
Derivation Cohort	HeartMate II LVAS	0.75	0.03	0.00	0.70	0.81
	HeartWare HVAD	0.67	0.02	0.00	0.63	0.71
	Thoratec - HeartMate 3	0.61	0.05	0.04	0.50	0.71
Validation Cohort	HeartMate II LVAS	0.70	0.04	0.00	0.62	0.77
	HeartWare HVAD	0.66	0.03	0.00	0.61	0.71
	Thoratec - HeartMate 3	0.56	0.08	0.38	0.42	0.71
a. Under the nonparametric assumption						
b. Null hypothesis: true area = 0.5						

Supplementary Table V. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the HeartMate II subgroup in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	97.1 - 100.0	0.00	0.0 - 0.5	1.00				15.5	13.1 - 18.2		
>0	92.74	86.7 - 96.6	21.15	18.1 - 24.4	1.18	1.0 - 1.4	0.34	0.2 - 0.6	17.7	14.9 - 20.9	94.1	89.1 - 97.3
>1	87.90	80.8 - 93.1	31.36	27.9 - 35.0	1.28	1.1 - 1.5	0.39	0.2 - 0.6	19.0	15.9 - 22.5	93.4	89.3 - 96.3
>2	72.58	63.8 - 80.2	71.30	67.7 - 74.7	2.53	2.2 - 2.8	0.38	0.3 - 0.5	31.7	26.3 - 37.4	93.4	90.9 - 95.4
>2.5*	72.58	63.8 - 80.2	71.45	67.9 - 74.8	2.54	2.3 - 2.9	0.38	0.3 - 0.5	31.8	26.4 - 37.6	93.4	90.9 - 95.4
>3	44.35	35.4 - 53.5	89.64	87.1 - 91.8	4.28	3.5 - 5.2	0.62	0.5 - 0.8	44.0	35.1 - 53.2	89.8	87.2 - 92.0
>4	37.90	29.3 - 47.1	92.31	90.0 - 94.2	4.93	3.9 - 6.2	0.67	0.5 - 0.9	47.5	37.3 - 57.8	89.0	86.5 - 91.2
>4.5	34.68	26.4 - 43.7	93.20	91.0 - 95.0	5.10	4.0 - 6.5	0.70	0.5 - 1.0	48.3	37.6 - 59.2	88.6	86.0 - 90.8
>5	20.16	13.5 - 28.3	96.30	94.6 - 97.6	5.45	3.8 - 7.7	0.83	0.6 - 1.2	50.0	35.5 - 64.5	86.8	84.2 - 89.1
>5.5	8.06	3.9 - 14.3	98.22	96.9 - 99.1	4.54	2.5 - 8.2	0.94	0.5 - 1.6	45.5	23.9 - 68.3	85.3	82.7 - 87.8
>6	7.26	3.4 - 13.3	98.22	96.9 - 99.1	4.09	2.2 - 7.7	0.94	0.5 - 1.7	42.9	21.3 - 66.6	85.2	82.5 - 87.7
>6.5	7.26	3.4 - 13.3	98.52	97.3 - 99.3	4.91	2.6 - 9.2	0.94	0.5 - 1.7	47.4	23.9 - 71.8	85.3	82.6 - 87.7
>7	4.84	1.8 - 10.2	98.67	97.5 - 99.4	3.63	1.7 - 7.9	0.96	0.5 - 1.8	40.0	16.3 - 67.7	85.0	82.3 - 87.4
>7.5	0.81	0.02 - 4.4	99.70	98.9 - 100.0	2.73	0.4 - 19.2	0.99	0.2 - 4.0	33.3	0.8 - 90.6	84.6	81.9 - 87.0
>9.5	0.00	0.0 - 2.9	100.00	99.5 - 100.0			1.00				84.5	81.8 - 86.9

Supplementary Table VI. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the HeartWare subgroup in the derivation cohort.

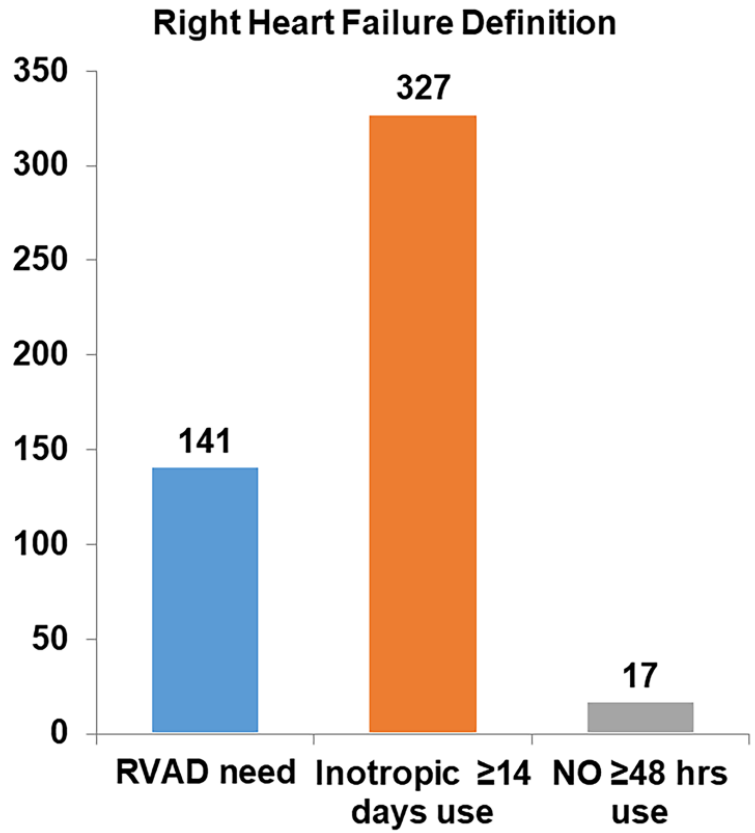
Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	98.5 - 100.0	0.00	0.0 - 0.5	1.00				24.1	21.5 - 26.9		
>0	94.65	91.0 - 97.1	15.84	13.3 - 18.6	1.12	1.0 - 1.3	0.34	0.2 - 0.6	26.3	23.5 - 29.4	90.3	84.0 - 94.7
>1	92.18	88.1 - 95.2	25.65	22.6 - 28.9	1.24	1.1 - 1.4	0.30	0.2 - 0.5	28.3	25.2 - 31.6	91.2	86.5 - 94.6
>2	77.78	72.0 - 82.8	45.03	41.5 - 48.6	1.41	1.3 - 1.6	0.49	0.4 - 0.6	31.0	27.4 - 34.9	86.4	82.7 - 89.6
>2.5	77.78	72.0 - 82.8	45.16	41.6 - 48.8	1.42	1.3 - 1.6	0.49	0.4 - 0.6	31.1	27.4 - 34.9	86.5	82.7 - 89.7
>3 *	50.21	43.7 - 56.7	73.04	69.7 - 76.2	1.86	1.6 - 2.1	0.68	0.6 - 0.8	37.2	31.9 - 42.7	82.2	79.1 - 85.0
>4	45.68	39.3 - 52.2	76.83	73.7 - 79.8	1.97	1.7 - 2.3	0.71	0.6 - 0.8	38.5	32.9 - 44.4	81.6	78.6 - 84.4
>4.5	42.80	36.5 - 49.3	79.19	76.1 - 82.0	2.06	1.8 - 2.4	0.72	0.6 - 0.9	39.5	33.6 - 45.7	81.3	78.3 - 84.1
>5	26.75	21.3 - 32.8	87.30	84.7 - 89.6	2.11	1.7 - 2.6	0.84	0.7 - 1.0	40.1	32.5 - 48.1	78.9	76.0 - 81.6
>5.5	17.28	12.7 - 22.6	94.90	93.1 - 96.3	3.39	2.6 - 4.5	0.87	0.6 - 1.2	51.9	40.5 - 63.1	78.3	75.5 - 80.9
>6	16.46	12.0 - 21.7	95.03	93.2 - 96.5	3.31	2.5 - 4.4	0.88	0.6 - 1.2	51.3	39.6 - 62.8	78.1	75.4 - 80.8
>6.5	14.40	10.2 - 19.5	95.42	93.7 - 96.8	3.14	2.3 - 4.3	0.90	0.6 - 1.2	50.0	37.7 - 62.3	77.8	75.0 - 80.4
>7	11.52	7.8 - 16.2	96.47	94.9 - 97.7	3.26	2.3 - 4.6	0.92	0.6 - 1.3	50.9	37.1 - 64.6	77.4	74.6 - 80.0
>7.5	0.82	0.10 - 2.9	99.74	99.1 - 100.0	3.14	0.8 - 12.5	0.99	0.2 - 4.0	50.0	3.9 - 96.1	76.0	73.2 - 78.6
>8.5	0.82	0.10 - 2.9	99.87	99.3 - 100.0	6.29	1.6 - 25.0	0.99	0.1 - 7.0	66.7	9.4 - 99.2	76.0	73.2 - 78.6
>9.5	0.00	0.0 - 1.5	100.00	99.5 - 100.0			1.00				75.9	73.1 - 78.5

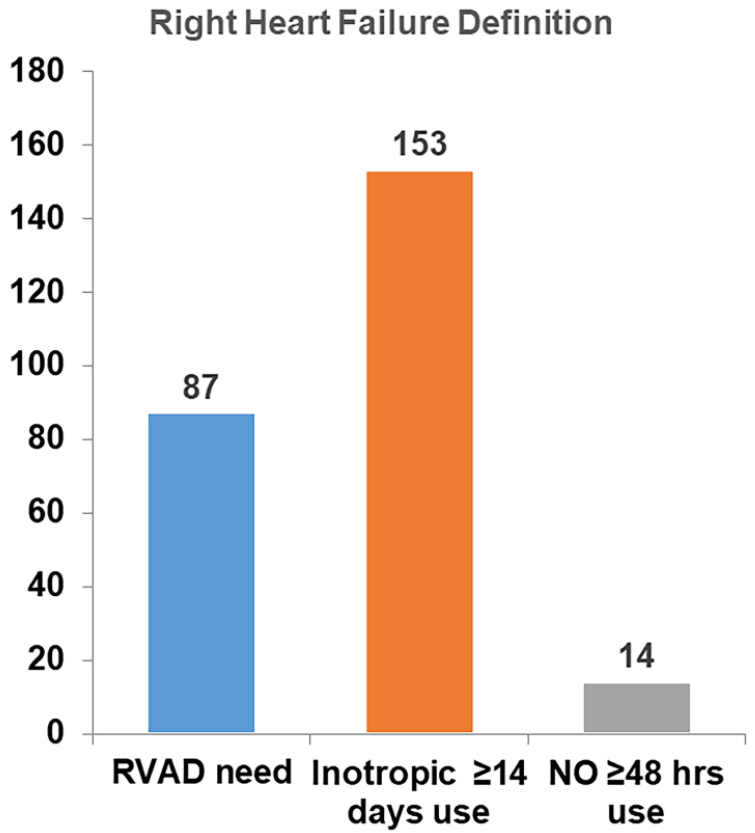
Supplementary Table VII. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value according to the EUROMACS-RHF risk score in the HeartMate 3 subgroup in the derivation cohort.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>=0	100.00	91.6 - 100.0	0.00	0.0 - 2.9	1.00				24.9	18.5 - 32.1		
>0	83.33	68.6 - 93.0	20.47	13.8 - 28.5	1.05	0.7 - 1.5	0.81	0.4 - 1.6	25.7	18.6 - 33.9	78.8	60.8 - 91.2
>1	76.19	60.5 - 87.9	24.41	17.2 - 32.8	1.01	0.7 - 1.4	0.98	0.6 - 1.7	25.0	17.8 - 33.4	75.6	59.7 - 87.6
>2	61.90	45.6 - 76.4	55.12	46.0 - 63.9	1.38	1.0 - 1.8	0.69	0.4 - 1.1	31.3	21.6 - 42.4	81.4	71.6 - 89.0
>3 *	35.71	21.6 - 52.0	85.04	77.6 - 90.7	2.39	1.6 - 3.6	0.76	0.5 - 1.2	44.1	26.9 - 62.4	80.0	72.3 - 86.4
>4	26.19	13.9 - 42.0	88.98	82.2 - 93.8	2.38	1.4 - 4.0	0.83	0.5 - 1.4	44.0	24.4 - 65.1	78.5	70.9 - 84.9
>5	16.67	7.0 - 31.4	97.64	93.3 - 99.5	7.06	3.6 - 13.9	0.85	0.3 - 2.6	70.0	32.8 - 94.1	78.0	70.7 - 84.2
>5.5	9.52	2.7 - 22.6	97.64	93.3 - 99.5	4.03	1.6 - 10.2	0.93	0.3 - 2.8	57.1	15.9 - 91.8	76.5	69.3 - 82.8
>6	7.14	1.5 - 19.5	99.21	95.7 - 100.0	9.07	3.0 - 27.0	0.94	0.1 - 6.6	75.0	13.2 - 99.8	76.4	69.1 - 82.6
>7	0.00	0.0 - 8.4	99.21	95.7 - 100.0	0.00		1.01	0.1 - 7.1	0.0	0.0 - 50.0	75.0	67.7 - 81.3
>7.5	0.00	0.0 - 8.4	100.00	97.1 - 100.0			1.00				75.1	67.9 - 81.5

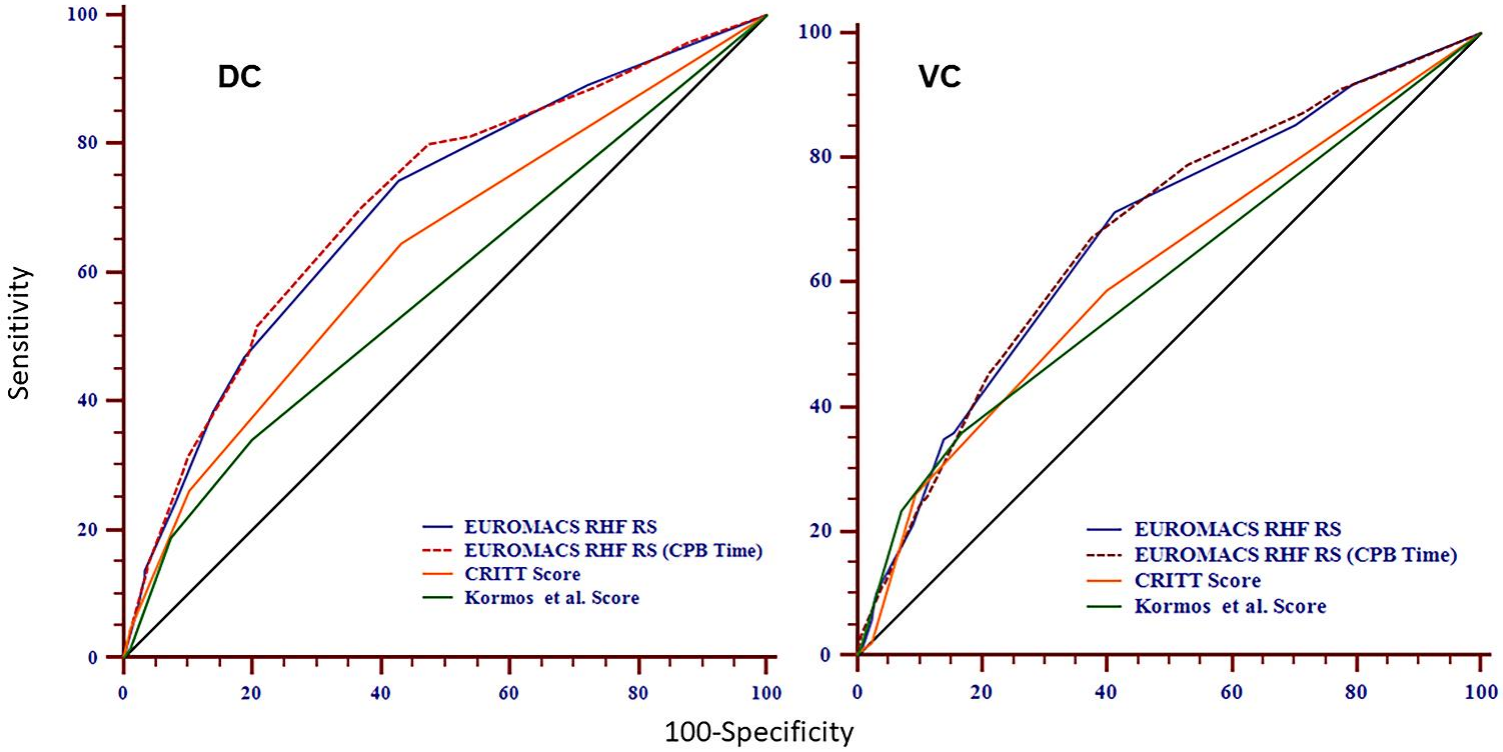
Supplemental Figures

Supplementary Figure I. Components of Right Heart Failure Definition in the derivation (left) versus validation (Right) cohort. Of note, total patients who had right heart failure = 433; some patients were already on inotropic support >14 days and received later an RVAD.





Supplementary Figure II. ROC Curve analysis derived from the derivation cohort (DC) and validation cohort (VC). ROC Curve of the EUROMACS RHF-Risk Score, postoperative modified (plus CPB time) EUROMACS RHF-Risk Score are compared with two published RHF risk scores derived from patients with continuous flow LVAD as well as the areas under the receiver operating characteristic (ROC) curve for the individual scores.



Supplementary Figure III. Percentage of Patients Receiving Inotropic Support in derivation cohort

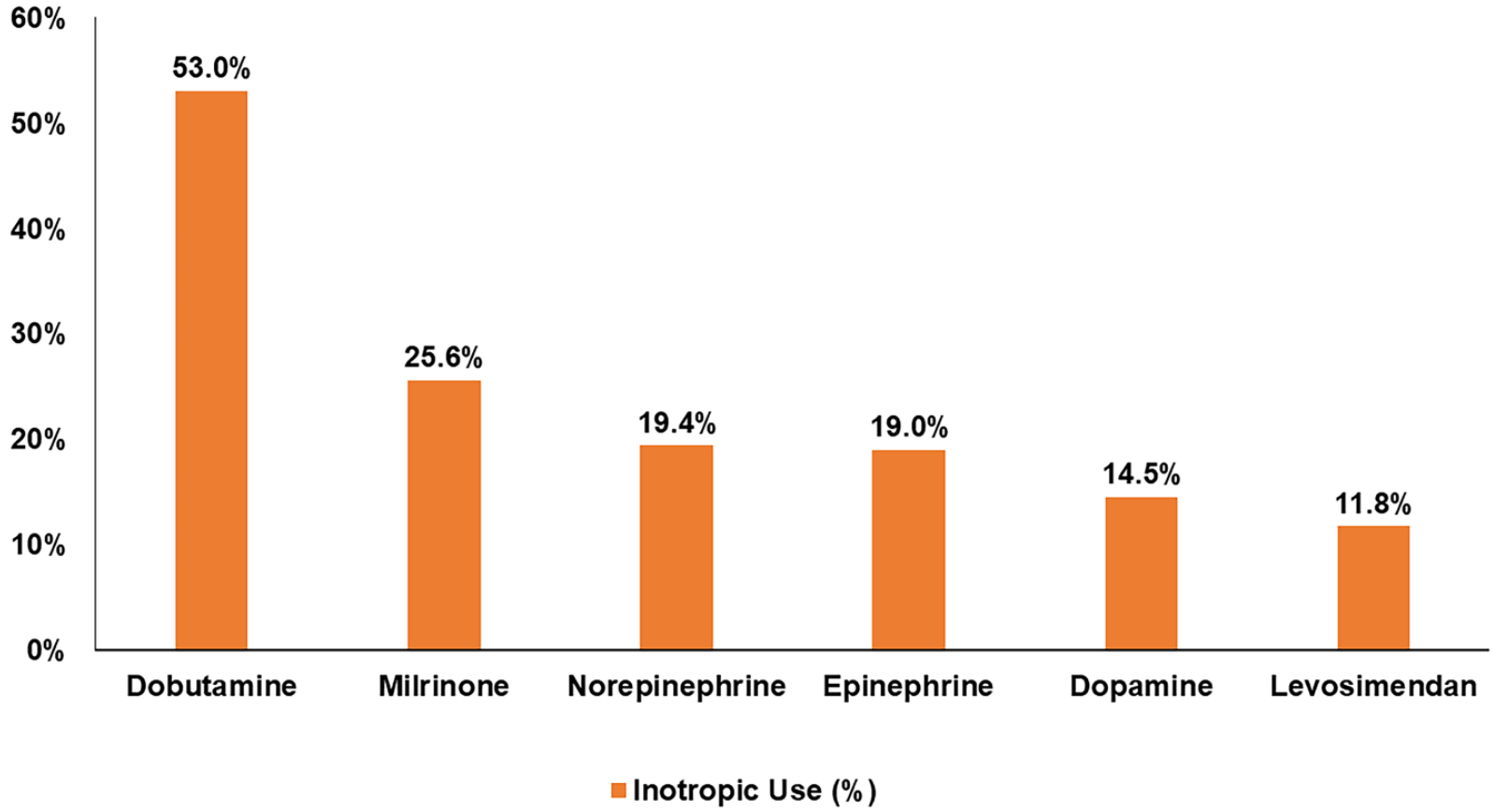


Figure Legends

Supplementary Figure I. Components of Right Heart Failure Definition in the derivation (left) versus validation (Right) cohort. Of note, total patients who had right heart failure = 433; some patients were already on inotropic support >14 days and received later an RVAD.

Supplementary Figure II. ROC Curve analysis derived from the derivation cohort (DC) and validation cohort (VC). ROC Curve of the EUROMACS RHF-Risk Score, postoperative modified (plus CPB time) EUROMACS RHF-Risk Score are compared with two published RHF risk scores derived from patients with continuous flow LVAD as well as the areas under the receiver operating characteristic (ROC) curve for the individual scores.

Supplementary Figure III. Percentage of Patients Receiving Inotropic Support in derivation cohort

Appendix I. List of EUROMACS sites and investigators (alphabetical according to country)

Name	City:	Country:	Representative
Universitätskliniken Innsbruck	Innsbruck	Austria	Prof. Herwig Antretter
Central Clinic Hospital	Baku	Azerbaijan	Prof. Kamran Musayev
National Institute "Cardiology"	Minsk	Belarus	Dr. Valeriya Krachak
Onze Lieve Vrouwenziekenhuis	Aalst	Belgium	Dr. Marc Vanderheyden
Universitair Ziekenhuis Gent	Gent	Belgium	Prof. Yves van Belleghem
Katholieke Universiteit Leuven	Leuven	Belgium	Prof. Bart Meyns
IKEM (Institute for Experimental Cardiac Surgery)	Prague	Czech Republic	Prof. Ivan Netuka
Center for Cardiovascular and Transplant Surgery	Brno	Czech Republic	Prof. Petr Nemec
Rigshospitalet Copenhagen	Copenhagen	Denmark	Prof. Finn Gustafsson
Centre Chirurgical Marie Lannelongue	Le Plessis-Robinson	France	Prof. Julien Guihaire
Deutsches Herzzentrum Berlin	Berlin	Germany	Prof. Thomas Krabatsch
Universitätsklinikum Schleswig Holstein	Lübeck	Germany	Prof. Stefan Klotz
Herz- und Diabeteszentrum Nordrhein-Westfalen	Bad Oeynhausen	Germany	Prof. Jan Gummert
Universitätsklinikum Eppendorf	Hamburg	Germany	Prof. Hermann Reichenspurner
Universitäts Herzzentrum Freiburg - Bad Krozingen	Freiburg	Germany	Prof. Friedhelm Beyersdorf
Klinikum Karlsburg	Karlsburg	Germany	Dr. Lutz Hilker
Aristotle University of Thessaloniki	Thessaloniki	Greece	Prof. Kyriakos Anastasiadis
Onassis Cardiac Surgery Center	Athens	Greece	Prof. George Stavridis
Heart Center of the Semmelweis University	Budapest	Hungary	Prof. Béla Merkely
Gottsegen Gy. Hungarian Institute of Cardiology	Budapest	Hungary	Dr. Gabor Bodor
Osepdale S. Orsola	Bologna	Italy	Prof. Roberto Di Bartolomeo
Ospedale San Camillo	Rome	Italy	Prof. Francesco Musumeci
Ospedale Niguarda Ca'Granda	Milan	Italy	Prof. Claudio Russo
Ospedale Papa Giovanni XXIII	Bergamo	Italy	Dr. Attilio Iacovoni
Ospedale dei Colli	Naples	Italy	Dr. Cristiano Amarelli
ISMETT (Mediterranean Institute for Transplantation and Advanced Specialised Therapies)	Palermo	Italy	Prof. Sergio Sciacca
Regina Margherita Children's Hospital	Torino	Italy	Prof. Carlo Pace Napoleone
National Research Cardiac Surgery Center - Kazakhstan	Astana	Kazakhstan	Prof. Yuri Pya
Erasmus Medisch Centrum	Rotterdam	Netherlands	Dr. Kadir Caliskan
Universitair Medisch Centrum Utrecht (UMCU)	Utrecht	Netherlands	Dr. Faiz Ramjankhan
Universitair Medisch Centrum Groningen (UMCG)	Groningen	Netherlands	Dr. Kevin Damman
Rikshospitalet	Oslo	Norway	Prof. Arnt Fiane
Childrens Memorial Hospital	Warsaw	Poland	Prof. Bodan Maruszewski
Silesian Center for Heart Diseases	Zabrze	Poland	Prof. Marian Zembala
Clínica Universidad de Navarra	Pamplona	Spain	Prof. Gregorio Rábago
Inselspital Bern	Bern	Switzerland	Prof. Paul Mohacsi
Kinderspital Zürich	Zürich	Switzerland	Prof. Michael Hübler
Ege University School of Medicine	Izmir	Türkiye	Prof. Mustafa Özbaran
Florence Nightingale Hospital	Istanbul	Türkiye	Dr. Erman Pektok
Başkent University Hospital	Ankara	Türkiye	Prof. Atilla Sezgin
Yüksek Ihtisas Hospital	Ankara	Türkiye	Prof. Ümit Kervan