



HAL
open science

Current results of left ventricular assist device therapy in France: the ASSIST-ICD registry

Amedeo Anselmi, Vincent Galand, André Vincentelli, Stéphane Boulé,
Camille Dambrin, Clément Delmas, Laurent Barandon, Mathieu Pernot,
Michel Kindo, Hoang Minh Tam, et al.

► To cite this version:

Amedeo Anselmi, Vincent Galand, André Vincentelli, Stéphane Boulé, Camille Dambrin, et al.. Current results of left ventricular assist device therapy in France: the ASSIST-ICD registry. *European Journal of Cardio-Thoracic Surgery*, 2020, 58 (1), pp.112-120. 10.1093/ejcts/ezaa055 . hal-02545980v2

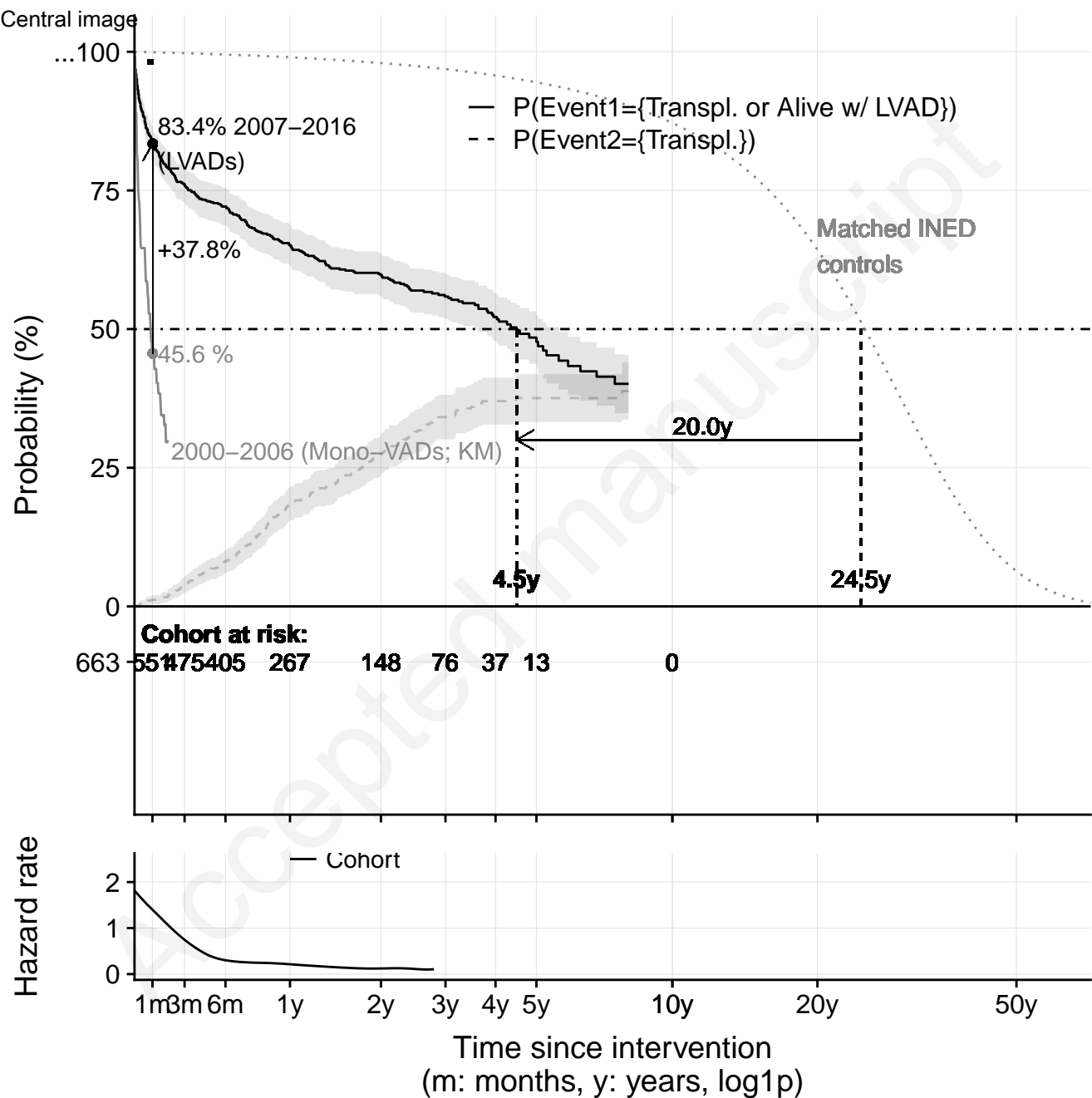
HAL Id: hal-02545980

<https://hal.science/hal-02545980v2>

Submitted on 10 Jun 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



CURRENT RESULTS OF LEFT VENTRICULAR ASSIST DEVICE THERAPY IN FRANCE: THE ASSIST-ICD REGISTRY

Amedeo ANSEMI¹, MD PhD, Vincent GALAND², MD, André VINCENNELLI³, MD PhD, Stéphane BOULE³, MD, Camille DAMBRIN⁵, MD, Clément DELMAS⁵, MD, Laurent BARANDON⁶, MD PhD, Mathieu PERNOT⁶, MD, PhD, Michel KINDO⁷, MD PhD, Tam HOANG MINH⁷, MD, Philippe GAUDARD⁹, MD, Philippe ROUVIERE¹⁰, MD, Thomas SENAGE¹¹, MD, Magali MICHEL¹¹, MD, Aude BOIGNARD¹², MD, Olivier CHAVANON¹², MD, Constance VERDONK¹³, MD, Marylou PARA¹³, MD, Vlad GARIBOLDI¹⁴, MD, Edeline PELCE¹⁴, MD, Matteo POZZI¹⁵, MD PhD, Jean-François OBADIA¹⁵, MD PhD, Frederic ANSELME¹⁶, MD PhD, Pierre-Yves LITZLER¹⁶, MD PhD, Gerard BABATASI¹⁷, MD PhD, Annette BELIN¹⁷, MD, Fabien GARNIER¹⁸, MD, Marie BIELEFELD¹⁸, MD, Julien GUIHAIRE¹⁹, MD PhD, Martin KLOECKNER²⁰, MD, Costin RADU²¹, MD, Nicolas LELLOUCHE²¹, MD, Thierry BOURGUIGNON²², MD, Thibaud GENET²³, MD, Nicolas D'OSTREY²⁴, MD, Benjamin DUBAND²⁴, MD, Jerome JOUAN²⁵, MD, Marie Cécile BORIES²⁵, MD, Fabrice VANHUYSE²⁶, MD, Hugues BLANGY²⁶, MD, Fabrice COLAS¹, PhD, Jean-Philippe VERHOYE¹, MD, PhD, Raphael MARTINS², MD PhD, MD PhD, Erwan FLECHER¹, MD PhD

On behalf of the Determination of Risk Factors of Ventricular Arrhythmias
After Implantation of Continuous Flow Left Ventricular Assist Device
(ASSIST-ICD) Investigators

¹Division of Thoracic and Cardiovascular Surgery, Univ Rennes, CHU Rennes, INSERM, LTSI - UMR 1099, F-35000 Rennes, France;

²Division of Cardiology, Univ Rennes, CHU Rennes, INSERM, LTSI - UMR 1099, F-35000 Rennes, France;

³CHU Lille, Institut Coeur-Poumons, Department of Cardiac Surgery, Lille, France;

⁴CHU Lille, Institut Coeur-Poumons, Department of Cardiology, Lille, France;

⁵Centre Hospitalier Universitaire de Toulouse, Toulouse, France;

⁶Hôpital Cardiologique du Haut-Lévêque, Université Bordeaux II, Bordeaux, France;

- 33 ⁷Département de chirurgie cardiovasculaire, hôpitaux universitaires de Strasbourg,
34 Strasbourg, France;
- 35 ⁹Department of Anesthesiology and Critical Care Medicine, PhyMedExp, University of
36 Montpellier, INSERM, CNRS, CHU Montpellier, Montpellier, France;
- 37 ¹⁰Department of cardiac surgery, University of Montpellier, CHU Montpellier, Montpellier,
38 France
- 39 ¹¹Department of Cardiology and Heart Transplantation Unit, CHU Nantes, France;
- 40 ¹²Department of Cardiology and Cardiovascular Surgery, CHU Michallon, Grenoble,
41 France;
- 42 ¹³Department of Cardiology and cardiac surgery, Bichat-Hospital, Paris, France;
- 43 ¹⁴Department of Cardiac Surgery, La Timone Hospital, Marseille, France
- 44 ¹⁵Department of Cardiac Surgery, "Louis Pradel" Cardiologic Hospital, Lyon, France;
- 45 ¹⁶Department of Cardiology and Cardiovascular Surgery, Hospital Charles Nicolle, Rouen,
46 France;
- 47 ¹⁷Department of Cardiology and Cardiac Surgery, University of Caen and University
48 Hospital of Caen, France;
- 49 ¹⁸Department of Cardiology and cardiac surgery, University Hospital François Mitterrand,
50 Dijon, France;
- 51 ¹⁹Department of Cardiac Surgery, Research and Innovation Unit, Inserm U999, Marie
52 Lannelongue Hospital, Paris Sud University, Le Plessis Robinson, France
- 53 ²⁰Department of Cardiac Surgery, Marie Lannelongue Hospital, Paris Sud University, Le
54 Plessis Robinson, France
- 55 ²¹Department of Cardiology and Cardiac Surgery, AP-HP CHU Henri Mondor, Créteil,
56 France;
- 57 ²²Department of Cardiac Surgery, Tours University Hospital, Tours, France;
- 58 ²³Department of Cardiology, Tours University Hospital, Tours, France;
- 59 ²⁴CHU Clermont-Ferrand, Cardiac Surgery and Cardiology Department, Clermont-Ferrand,
60 France;
- 61 ²⁵European Georges Pompidou Hospital, Cardiology Department, Paris, France;
- 62 ²⁶Department of Cardiology and Cardiac Surgery, CHU de Nancy, Hopital de Brabois,
63 Nancy, France.
- 64
- 65

66 **Address for correspondence:**

67 Amedeo Anselmi, MD, PhD
68 Division of Thoracic and Cardiovascular Surgery
69 Pontchaillou University Hospital – Rennes, France
70 E-mail amedeo.anselmi@chu-rennes.fr
71 Telephone: 00 33 2 99 28 24 16
72 Fax: 00 33 2 99 28 24 96
73

74 WORD COUNT: 5,430

75

76

77

78

79 **Abstract**

80 **Objective.** Provide a picture of LVAD activity in France between 2007 and 2016 based on
81 the multicentric ASSIST-ICD Registry.

82 **Methods.** We retrospectively collected 136 variables including in-hospital data, follow-up
83 survival, and adverse events over N=671 LVAD recipients at 20 out of 24 LVAD-implanting
84 centers in France. The average follow-up was 1.2 years (SD: 1.4) and the total follow-up
85 was 807.5 patient-years.

86 **Results.** The included devices were HeartMate II®, HeartWare LVAS® or Jarvik 2000®.
87 The overall likelihood of being alive under LVAD support or transplanted (primary
88 endpoint) at 1-, 2-, 3- and 5-years post-implantation was 65.2%, 59.7%, 55.9%, and
89 47.7%, given a cumulative incidence of being transplanted at year 5 of 29.2%. At
90 implantation, 21.5% of patients were on ECLS. The overall rate of cardiogenic shock at
91 implantation was 53%. The major complications were driveline infection (26.1%), pump
92 pocket or cannula infection (12.6%), LVAD thrombosis (12.2%), ischemic (12.8%) or
93 hemorrhagic stroke (5.4%; all strokes 18.2%), noncerebral hemorrhage (9.1%), and LVAD
94 exchange (5.2%). The primary endpoint (survival) stratified by age at surgery and by type
95 of device employed, with inference from baseline profile. The primary endpoint combined
96 with an absence of complications (secondary endpoint) also stratified by device type.
97 **Conclusions.** The ASSIST-ICD registry provides a real-life picture of LVAD use in 20 of
98 the 24 implanting centers in France. Despite older average age and higher proportion of
99 destination therapy patients, survival improved as compared to previous national registry
100 results. This LVAD registry contrasts with other international registries as implanted
101 patients are more severe and national policy for graft attribution is distinct. We recommend
102 to refer LVAD patients earlier and suggest to discuss the optimal transplantation timing e
103 of bridged patients (more dismal results after the second year of support?).

104

105

106

107 **KEYWORDS:** Left Ventricular Assist Devices; Outcomes; Temporal Trends

108

109

110

111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135

Introduction.

While heart transplantation remains the gold standard treatment for end-stage heart failure, long-term mechanical circulatory support (MCS) emerged as a viable option both for bridge-to-transplant patients and patients not amenable to transplantation. Following the encouraging results of first generation devices [1], second generation Continuous-Flow Left Ventricular Assist Devices (CF-LVADs) improve on survival and functional status [2]. In this context, the group for reflection on mechanical circulatory assistance (GRAM, *Groupe de Réflexion sur l'Assistance Mécanique*) published in 2011 a landmark report over MCS in France over the 2000-2005 period [3]. Later, the ASSIST-ICD registry was setup to investigate ventricular arrhythmias under CF-LVAD in France between 2007 and 2016. However, this registry turned out to also be a unique appraisal of LVAD activity throughout France between 2007 and 2016, even though it wasn't conceived as a follow-up to the GRAM database. As a result, based on the ASSIST-ICD registry, we herein provide trends, results, and specificities of LVAD therapy in France with respect to previous data and international practice.

136 **Patients and Methods.**

137 Data collection and management of the ASSIST-ICD registry

138 ASSIST-ICD (determination of risk factors of ventricular arrhythmias (VAs) after
139 implantation of continuous flow left ventricular assist device) is an observational,
140 retrospective, single-cohort, multi-center registry. Initially, it was conceived to help
141 decision-making in arrhythmology and cardiac electrophysiology by studying late
142 ventricular arrhythmias, survival, death causes, indications, effectiveness, and implantable
143 cardioverter defibrillator (ICD) therapy complications in LVAD patients.

144 The registry includes patients aged 18 or older at implantation, primary-implanted
145 between January 2007 and December 2016, and with one of three CF-LVADs, i.e.,
146 HeartMate II (Abbott Inc., Chicago, IL), HeartWare HVAD (Medtronic Inc., Minneapolis,
147 MN), or Jarvik 2000 LVAD (Jarvik Heart Inc., New York, NY). The registry excludes
148 patients having a total artificial heart, a pulsatile LVAD, having any device other than those
149 mentioned above, and being heart transplanted before LVAD support.

150 The ASSIST-ICD register was approved by local ethical committees, the French advisory
151 committee on the treatment of research data in healthcare, and France's data protection
152 authority (CNIL, *Commission Nationale de l'Informatique et des Libertés*). It is recorded as
153 NCT02873169 in the ClinicalTrials.gov database. As required by French authorities for
154 retrospective studies, we collected non-opposition letters from patients. Over 24
155 cardiothoracic centers implanting LVADs in adult patients in France, 20 (83%) contributed
156 to the registry. In this report, as compared to our previous publication [4], our analysis
157 features herein one more center (Marie Lannelongue Hospital).

158 The registry describes patients with 136 pre-, intra-, and post-operative variables, which
159 we collected retrospectively from hospital records. According to each center's protocol, we
160 conducted follow-up through outpatient visits and recurrent hospitalizations (if applicable).
161 Individual teams managed antithrombotic therapy under LVAD. Multidisciplinary teams

162 performed systematic follow-up according to local organizational settings. The study's
163 latest follow-up was December 31st, 2016.

164

165 Left Ventricular Assist Devices

166 As mentioned previously, included patients received one of three CF-LVADs, i.e.,
167 HeartMate II, HeartWare HVAS, or Jarvik 2000 LVAD. We've included patients irrespective
168 of the surgical approach, i.e., median sternotomy, left posterolateral thoracotomy, or left or
169 right mini invasive thoracotomy. We also bring up that reimbursement policy between
170 devices did not differ, that implanting teams were free to choose the device in each case,
171 and that there's no formal recommendation to choose between LVAD types in France. We
172 describe the number of LVAD implanted per year and per model in Figure 1.

173

174 Endpoints

175 In this report, as transplantation competes with survival under LVAD, we primarily report
176 results on the event: being alive under LVAD support or transplanted (i.e., not dying under
177 LVAD support), thereby focusing the analysis on the patient's long-term outcome. Then,
178 we define the secondary endpoint as the composite event: having no major complication
179 and, the primary endpoint, being alive under LVAD or transplanted. The third endpoint
180 illustrates recent national trends in CF-LVAD therapy. We define early outcomes as
181 occurring within the 30th post-operative day or later (if during the same hospitalization). We
182 include all later events in the follow-up analysis.

183

184 Statistical Analysis

185 We describe continuous data with the mean and the standard deviation (SD). We report
186 counts and proportions for categorical and ordinal data. For continuous variables we test

187 for differences using the Mann–Whitney U test. For categorical or ordinal variables we use
188 the Chi-Squared or the Fisher's Exact test when a cell-count is less than 5.

189 To describe death etiology we report actual frequency estimates. Given the competing
190 risk of transplantation, we estimate the primary endpoint's probability (alive under LVAD
191 support or transplanted) as the complement of the cumulative incidence of dying under
192 LVAD support. We compute instantaneous hazard rates for primary and secondary
193 endpoints with Epanechnikov's kernel function and a local-bandwidth at each grid-point.

194 To compare cumulative incidence per group we use the log-rank test. To visualize
195 survival evolution by era, next to our cohort's primary endpoint (LVAD-only; N=671) we
196 overlay Mazzucotelli et al.'s cohort survival (mostly left mono-VADs; N=133) [3]. We draw
197 up that few transplantations have occurred yet in that early period, thereby allowing us to
198 neglect the influence of the competing risk due to transplantation. We also compare our
199 cohort against the lifetable's expected survival, matched for gender, age, and intervention-
200 year, from the French institute for demographic studies (INED). In this case we use the
201 one sample log-rank test [4]. Statistical analyses are done with R 3.5.0.

202

203 **Results.**

204 Early Results

205 Between 2007 and 2016, N=671 patients received an LVAD at the 20 French centers,
206 which represents 33 (SD: 3.9) devices per center in average. While 25% percent of the
207 centers implanted all three devices, 45% implanted two, and 30% used only one. Table 1
208 depicts the pre-implantation characteristics of the registry.

209 Our registry has 70.5% of HeartMate II, 18.9% of HeartWare, and 10.6% of Jarvik 2000.
210 In average, LVAD-patients staid 25.8 days (SD: 50.9) at the intensive care unit (ICU) and
211 50.9 days (SD: 37.1) at the hospital. We infer that LVAD-recipients often had severe
212 cardiogenic shock before LVAD implantation, because 29.2% had at least one modality of

213 transient MCS (ECLS, IABP, or Impella) and 21.5% had ECLS. Average levels of serum
214 creatinine (129.8 $\mu\text{mol/L}$) and blood bilirubin (23.2 mg/dL) suggest severe patient profiles
215 having variable degrees of end-organ failure. To manage severe right ventricular
216 dysfunction, 12.5% of the patients had early ECLS after LVAD implantation and temporary
217 right heart MCS. Hospital mortality at 30 days is 16.6% (SD: 1.9) mortality. Figure 2
218 details the study's flowchart.

219

220 Follow-up results

221 We observe an average follow-up duration of 1.2 years (SD: 1.4) with 807.5 patient-
222 years available for analysis and no patient lost at follow-up. Estimates of the primary
223 endpoint (alive under LVAD support or being transplanted) at 1-, 2-, 3- and 5 years after
224 implantation are 65.2%, 59.7%, 55.9%, and 47.7% respectively. The central Figure
225 illustrates the primary endpoint probability in the overall cohort along with the hazard rate.
226 Hazard is greatest during the three postoperative months, but after six months it plateaus
227 until the end of the second post-implantation year when it increases again.

228 As compared to the previous GRAM report [3], whose patient survival for the
229 univentricular assistance cohort is overlaid in the central Figure, our patient's early survival
230 (30 days) under LVAD increased dramatically from 45.6% to 83.4%. Nevertheless, due to
231 the severity of cardiovascular diseases in advanced heart failure patients, the registry's
232 median life expectancy is 20 years lower ($p < 0.001$) than France's national life table.

233 In terms of death etiology, the registry records 130 cases of cardiac deaths (19.4%) of
234 which we consider 55 (8.2%) right ventricular failures, 31 (4.6%) LVAD thromboses, 22
235 (3.3%) malignant ventricular arrhythmia, 3 (0.4%) cardiac tamponade, and 3 (0.4%) LVAD
236 failures. In terms of extracardiac deaths, the registry totals 13 (1.9%) deaths due ischemic
237 stroke, 35 (5.5%) due to hemorrhagic stroke, 19 (2.8%) due to other hemorrhage, 8 (1.2%)

238 due to mesenteric ischemia, 5 (0.7%) due to respiratory insufficiency, 48 (7.1%) due to
239 septic shock, 15 (2.2%) due to multiorgan failure, and 4 (0.6%) due to other causes.

240 In terms of LVAD-related complications, as reported in Table 2 the registry records
241 driveline (26.1%) and pump pocket or cannula infections (12.7%), LVAD thromboses
242 (12.5%), ischemic (12.8%) and hemorrhagic strokes (5.5%—all strokes rate 18.2%), TIA
243 (0.9%), noncerebral hemorrhages (12.8%), and LVAD exchange (5.2%). The six reasons
244 for LVAD exchange are LVAD thrombosis (62.9%), LVAD dysfunction (14.3%), LVAD
245 cannula infection (5.7%), aortic thrombosis (2.9%), LVAD cannula displacement (2.9%),
246 and other reasons (11.4%). In average the delay from LVAD implantation to LVAD
247 thrombosis was 7.6 months, to first stroke was 3 months, and to first bleeding was 4.1
248 months. During follow-up 196 patients (29.2%) received heart transplantation. The
249 average time between LVAD implantation and heart transplant was 150 days (4.9 months).

250 Figure 3 Panel C shows that age at implantation (less than 54, between 55 and 64, older
251 than 65) affects the likelihood of being alive under LVAD or transplanted ($p < 0.001$), with
252 youngest patients having the best outcome. Hazard rates suggest that the risk increase in
253 older individuals is essentially driven by the first six post-implantation months.
254 Subsequently, hazard rates are similar until they increase again after the second post-
255 implantation year, notably for older patients. The latter increase is likely due to the greater
256 fragility of older patients, which leads to more complications under support and
257 complication-related mortality.

258 Figure 3 Panel D suggests significant differences per device type ($p < 0.001$), with
259 HeartMate II recipients presenting better likelihood of being alive under LVAD or
260 transplanted than HeartWare HVAS and Jarvik 2000 recipients. However, recipient
261 characteristics differ significantly between device types, e.g., the average age at
262 implantation is 57.3 years for HeartMate II recipients, 56.7 for HeartWare HVAD, and 62.5
263 for Jarvik 2000 ($p < 0.01$), while indication as destination therapy is 33.6% for HeartMate II,

264 37.8% for HeartWare HVAD, and 74.6% for Jarvik 2000 ($p<0.01$). Additionally, these
265 differences subtend the survival disadvantage associated with no option for transplantation
266 and, likely, heterogeneous degrees of baseline comorbidities among subgroups. Figure 3
267 Panel E suggests a mild difference between LVAD types for the secondary endpoint, i.e.,
268 being alive under LVAD, transplanted, and having no major complication ($p=0.015$) but,
269 like previously, age or indication tend to confound the observed difference.

270

271

272

273 **Discussion.**

274 Originally, the ASSIST-ICD registry aimed to rationalize the use of implantable
275 cardioverter-defibrillators in LVAD-recipients. This initial work resulted in the VT-LVAD
276 score to predict the risk of malignant ventricular arrhythmias [5]. However, given the large
277 adherence to this registry among French centers implanting LVADs (20 out of 24), the
278 number of variables ($N=136$), the number of patients ($N=671$), and the follow-up era (2007
279 to 2016), the ASSIST-ICD registry emerged as a picture of LVAD activity in France. We
280 therefore discuss herein the major LVAD-related descriptors and outcomes.

281

282 Comparison with previous experience in France

283 Using data from the GRAM, whose important seminal work we acknowledge, a report of
284 2011 published results about long-term mechanical circulatory assistance in France
285 between 2000 and 2006 [3]. Here we compare our register to this earlier report.

286 Our patients are older at implantation (57.7 vs. 43.7 years) and fewer (58.4% vs. 87.9%)
287 are implanted as a bridge-to-transplant ($p<0.001$). We attribute these differences to
288 technological evolution (recent CF-LVADs becoming available), better knowledge, and

289 better management capabilities, which help apply MCS to older patients and use LVADs
290 as a destination therapy. Our registry shows lower in-hospital mortality (16.6% vs. 45.6%)
291 than the previous report's entire and univentricular support cohorts ($p < 0.001$, central
292 Figure), which we may explain by the exclusion of the more severe biventricular failure
293 patients and the use of second- and third-generation CF-LVADs that better-perform first-
294 generation CF-LVADs and pulsatile-flow LVADs.

295 In the GRAM registry the incidence of death at follow-up was lowest between three and
296 six months after implantation, and tended to increase at later timepoints. Here we report a
297 stable hazard rate between the sixth and the 24th post-operative months, irrespective of
298 patients' age (Figure 3 Panel C). Remarkably, the UNOS database shows results similar to
299 those of our registry [9]. We attribute the stable hazard rate to the better technology, the
300 better post-operative medical management, and the standardized practices [7, 8].

301 We infer from these results that transplantation efficacy could improve if it was
302 performed during the second post-implantation year, which may have major implications
303 for the attribution of priority on list for heart transplantation. Moreover, as pre-implantation
304 end-organ dysfunction is a known predictor of worse outcomes [10], we think that
305 accelerating referral before organ failure or right ventricular dysfunction could improve
306 patients' outcome.

307 Recent years have been characterized by expanding role of ECLS for the management of
308 more severe cases of cardiogenic shock (INTERMACS class I-II). Although ECLS
309 effectiveness is itself affected by baseline patient condition [11], it improves end-organ
310 function and helps gain time for reflection in complex patients ('bridge-to-bridge' concept).
311 Several studies show similar survival-rates under LVAD as those observed in
312 INTERMACS class III-IV patients [12, 13, 14].

313

314 *Specificities in France of LVAD support and heart transplantation policy*

315 In 2004, to prioritize the attribution of cardiac grafts to patients under unweanable short-
316 term mechanical circulatory assistance (ECLS) (degree 1) or to patients affected by
317 complications under LVAD support (degree 2), France puts in place the national super-
318 urgency system [15], which yielded fewer severe, ECLS-assisted patients undergoing
319 long-term MCS, but also a better management of severe LVAD-related complications like
320 pump pocket infections or pump thrombosis.

321 The proportion of transplanted patients in our registry is therefore remarkably lower than
322 in the GRAM report (29.2% vs 47.9%). Our patients are also less likely to receive an
323 LVAD as a bridge-to-transplant than in the previous GRAM report (87.9% vs 58.4%,
324 $p < 0.01$) [3], which further contrasts with the EUROMACS cohort that only reports 28% of
325 bridge-to-transplants [16]. Nevertheless, the INTERMACS database confirms the
326 development of LVAD as a destination therapy since 50% of CF-LVADs implantation were
327 for destination therapy in 2015, whereas bridge-to-transplantation and bridge-to-candidacy
328 lowered to 26% and 23% more recently [17].

329 The historical one-year survival after heart transplantation is 75.2% in France [18], while
330 for LVAD-recipients this survival was 78.6% between 2013 and 2015. In contrast, the
331 ISHLT database reports an 84% one-year survival after heart transplantation between
332 2006 and 2011, while considering a prior CF-LVAD implantation as an operative risk factor
333 [19]. Additional reports suggest that previous cardiac surgery is linked with lower survival
334 after transplantation [20]. Therefore, it matters to attentively select and prepare
335 candidates, optimize follow-up under LVAD to limit complications, and to keep evaluating
336 current CF-LVADs which are expected to provide better biocompatibility and quality of life.

337 Recent studies (second and third generation LVADs) fail to confirm the negative effect
338 of previous LVAD therapy on survival after transplantation [21]. As a specific feature of the
339 French national database, the best one-year survival after transplantation was observed
340 among patients suffering from LVAD complication (80.1%) vs. patients transplanted for

341 other national priorities (75.5%), or without priority (75.1%). [18]. This needs to be
342 considered by Heart Teams in the decision of timing of LVAD implantation in patients who
343 deteriorate while on transplantation list.

344 At LVAD implantation, 29.2% of our patients were on temporary MCS (corresponding to
345 INTERMACS classes I and II), whereas 53% were in cardiogenic shock. Although our
346 register misses INTERMACS classification, these rates indicate a high proportion of high
347 (I-II) INTERMACS profiles in our series. In the EUROMACS, the proportion of
348 INTERMACS I patients was 12.1% in 2015 and 14% in 2017 [16, 22], therefore our
349 registry would differ from the EUROMACS, which would explain some of the one-year
350 survival difference between our registry (65.2%) and the EUROMACS (69%). Similarly, in
351 the INTERMACS registry the rate of INTERMACS I patients ranges between 14 and 16%
352 since 2008, and their one-year survival on CF-LVAD is 81%.

353 Major controlled trials over LVAD therapy tend to focus on less severe populations, e.g.,
354 in the MOMENTUM 3 study [23] the rate of INTERMACS 1 profile was 0.8%. This feature
355 is likely at the root of the markedly better survival in both MOMENTUM 3 cohorts [24] than
356 in our registry. Also, this should be considered while comparing data with other published
357 databases.

358 The current healthcare management policy in France includes extensive access of
359 cardiogenic shock patients to ECLS as a bridge to recovery or bridge to decision. Along
360 with dedicated hospital networks, France has 60 ECLS-implanting centers. Besides, E-
361 CPR, i.e., ECLS for refractory cardiac arrest, is relatively diffuse. While indications for E-
362 CPR were refined over time [25], E-CPR remains effective in selected cases, helping
363 support the more challenging patients over the longer-term.

364 If we observe a significantly different survival under support by type of device (Figure 3
365 Panel D), this difference may result from differences in baseline patient profiles, e.g.,
366 different distribution of destination therapy strategy, which are more frequent among Jarvik

367 2000 vs. HeartMate II recipients. The distribution of complications and death causes also
368 confirms the importance of neurological events as a drawback of LVAD therapy [7, 26, 27].
369 To reduce the risk of pump thrombosis and stroke during initial follow-up, several new
370 devices were proposed [28]. If those risks are indeed reduced, those results should be
371 discussed along with the proposal to lower INTERMACS classes (3-4) of CF-LVAD
372 therapy, i.e., destination therapy indications. However, to tackle the under-referral problem
373 and better the patients' outcome, structured heart failure territorial networks and referral
374 teams are also necessary. Optimal antithrombotic management under LVAD remains an
375 open issue, too. If recent trials compare different antithrombotic strategies [29], such
376 analysis is beyond the scope of this report.

377 At 30-days, center-volume analysis shows some heterogeneity (Figure 3 Panel A and
378 Figure 4), but linear regression does not reveal any significant trend between center size
379 and early survival ($p=n.s.$). Nonetheless, in view of previous research suggesting that
380 higher volume centers tend to perform better [6], we need to carry out additional analyzes
381 to correctly interpret this aspect, e.g., by adjusting for the patients' baseline profile.

382 Limitations.

383 Despite a large participation of French implanting centers, not all of them were actually
384 involved, which we may explain by the different initial purposes of the current registry, i.e.,
385 electrophysiology-related issues in LVAD recipients. Therefore, the ASSIST-ICD registry
386 isn't fully representative of LVAD activity in France. Then, even though we used common
387 data collection mechanisms, variable definitions, and a centralized analysis, our registry
388 remains retrospective by design. We lack specific information like the INTERMACS class
389 and the rate of temporary right heart MCS for severe right ventricular failure occurring later
390 than arrival in the ICU. As well, we don't have statistics or reasons about LVAD-candidates
391 who were denied LVAD at implanting centers.

392 Conclusions.

393 The ASSIST-ICD registry provides a picture of recent (2007-2016) CF-LVAD activity in
394 France. A real-life context is described, as all-comers inclusion criteria were adopted. As
395 compared to previous historical periods, the main trends in France include increased
396 average age of candidates, expanding use as a destination therapy, and better survival of
397 the assisted patients. Evolving technology, better pre- and post-operative management,
398 and the specific heart transplantation access policy in France lie among the reasons for
399 such observation. The framework includes even access to long-term MCS, even for
400 patients affected by advanced cardiogenic shock, a liberal use of ECLS (national
401 healthcare strategy and reimbursement rules). We recommend earlier referral to LVAD.

402

403

404

405

406

407

408

409

410

411

412

413

414

415

416

417

418

419 **Acknowledgements.**

420 French Federation of Cardiology.

421

422 **Funding Statement.**

423 The present study was funded by the French Federation of Cardiology.

424

425 **Conflict of Interest.**

426 None.

427

428

429

430

431

432

433

434

435

436

437

438

439

440

441

442

443 Figure Legends.

444 **Figure 1. Panel A:** Yearly distribution of the number of implanted patients. **Panel B:**
445 Yearly distribution of implanted devices.

446 **Figure 2.** Study flowchart.

447 **Figure 3.** Probability of the primary (alive under LVAD support or transplanted) or
448 secondary endpoint (complication-free, alive under LVAD support, or transplanted) where
449 bands characterize the 95% confidence interval, number of at risk patients, and hazard
450 rate of the primary or secondary endpoint. The x-axis represents the time from surgical
451 intervention. It follows a logarithmic scale. **Panel A:** Primary endpoint stratified per center
452 size. **Panel B:** Primary endpoint stratified per gender. **Panel C:** Primary endpoint stratified
453 per age at implantation, i.e., younger than 55, between 55 and 65; older than 65. **Panel D:**
454 Primary endpoint stratified per type of LVAD. **Panel E:** Secondary endpoint stratified per
455 type of LVAD.

456 **Figure 4.** Actual probability of 30-day survival according to center-size (funnel plot with
457 95% and 99% confidence intervals)

458 Central Image Legend.

459 Between 2007 and 2016 in 20 out of 24 LVAD-implanting centers in France, probability of
460 being alive under LVAD support or transplanted posterior to LVAD-implantation in the
461 overall cohort (N=671).

462

463

464

465

466

467

468 **Table 1.** Baseline (before LVAD implantation) characteristics of the registry population.

Characteristic	
Age (years)	57.7 (SD: 11.5)
Gender (male)	576 (85.8%)
BMI (kg/m ²)	25.8 (SD: 4.7)
<u>Etiology of Cardiomyopathy</u>	
- Ischemic	418 (62.3%)
- Dilated idiopathic	187 (27.9%)
- Myocarditis	11 (1.6%)
- Cardiac valvopathy	9 (1.3%)
- Congenital cardiopathy	3 (0.4%)
- Other	43 (6.4%)
Heart failure duration (years)	8.4 (SD: 11.4)
ICD before LVAD	413 (31.5%)
CRT before LVAD	201 (29.9%)
History of supraventricular tachycardia	310 (46.2%)
LVEF (%)	20.5 (SD: 7.6)
LVEDD (mm)	69.5 (SD: 10.5)
LVEDV (mL)	247.5 (SD: 95.1)
PASP (mmHg)	50.3 (SD: 15)
TAPSE (mm)	16.2 (SD: 4.4)
Average tricuspid regurgitation degree (/4)	1.5 (SD: 1.0)
Right Atrial Pressure (mmHg)	10 (SD: 5.9)
PVR (Woods Units)	3.7 (SD: 7.3)
Serum creatinine (μmol/L)	129.8 (SD: 82.8)
Total bilirubin (mg/dL)	23.2 (SD: 78.2)
Hypertension	245 (36.5%)
Diabetes mellitus	164 (24.4%)
<u>Temporary circulatory support before LVAD</u>	
- Impella®	64 (9.5%)

- IABP	59 (8.8%)
- ECLS	144 (21.5%)
<u>Indication to LVAD therapy</u>	
- Bridge to Transplantation	392 (58.4%)
- Destination	260 (38.7%)
- Bridge to Recovery / Decision	6 (0.9%)
- Other	13 (1%)
<u>Associated procedure at LVAD implantation</u>	104 (15.5%)

469 *BMI: Body Mass Index. ICD: Implantable Cardioverter-Defibrillator. CRT: Cardiac*
470 *Resynchronization Therapy. IABP: Intra-Aortic Balloon Pump. ECLS: Extracorporeal Life*
471 *Support. LVEF: Left Ventricular Ejection Fraction. LVEDD: Left Ventricular End-Diastolic*
472 *Diameter. LVEDV: Left Ventricular End-Diastolic Left Ventricular End-Diastolic Volume.*
473 *PASP: Pulmonary Artery Systolic Pressure. TAPSE: Tricuspid Annular Plane Systolic*
474 *Excursion. PVR: Pulmonary Vascular Resistance.*

475

476

477

478

479

480

481

482

483

484

485

486

487

488

489

490

491

492

493 **Table 2.** Complications on LVAD support during the follow-up.

Characteristic	
<u>LVAD-related infection</u>	
- Driveline infection	175 (26.1%)
- Pump pocket / canula infection	85 (12.7%)
LVAD thrombosis	84 (12.5%)
LVAD replacement	35 (5.2%)
Ischemic stroke	86 (12.8%)
TIA	6 (0.9%)
Cerebral bleeding complications	37 (5.5%)
Noncerebral bleeding	86 (12.8%)

494

495

496

497

498

499

500

501

502

503

504

505

506

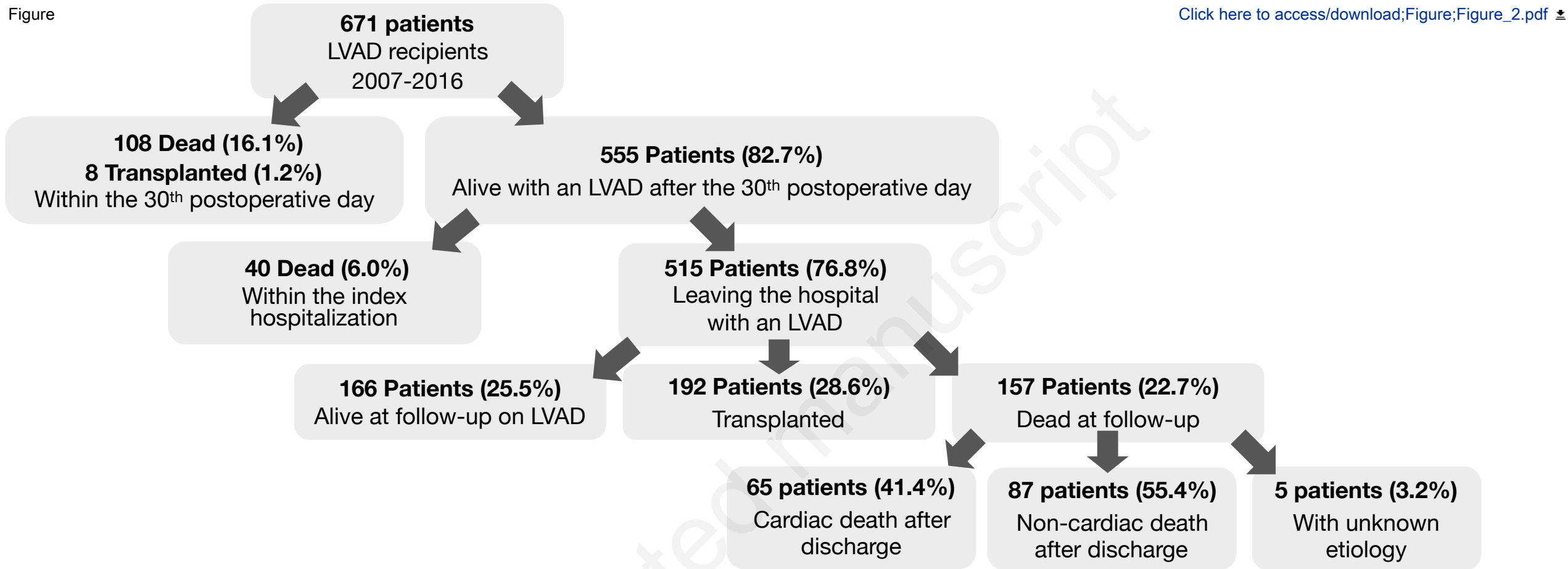
507 **References**

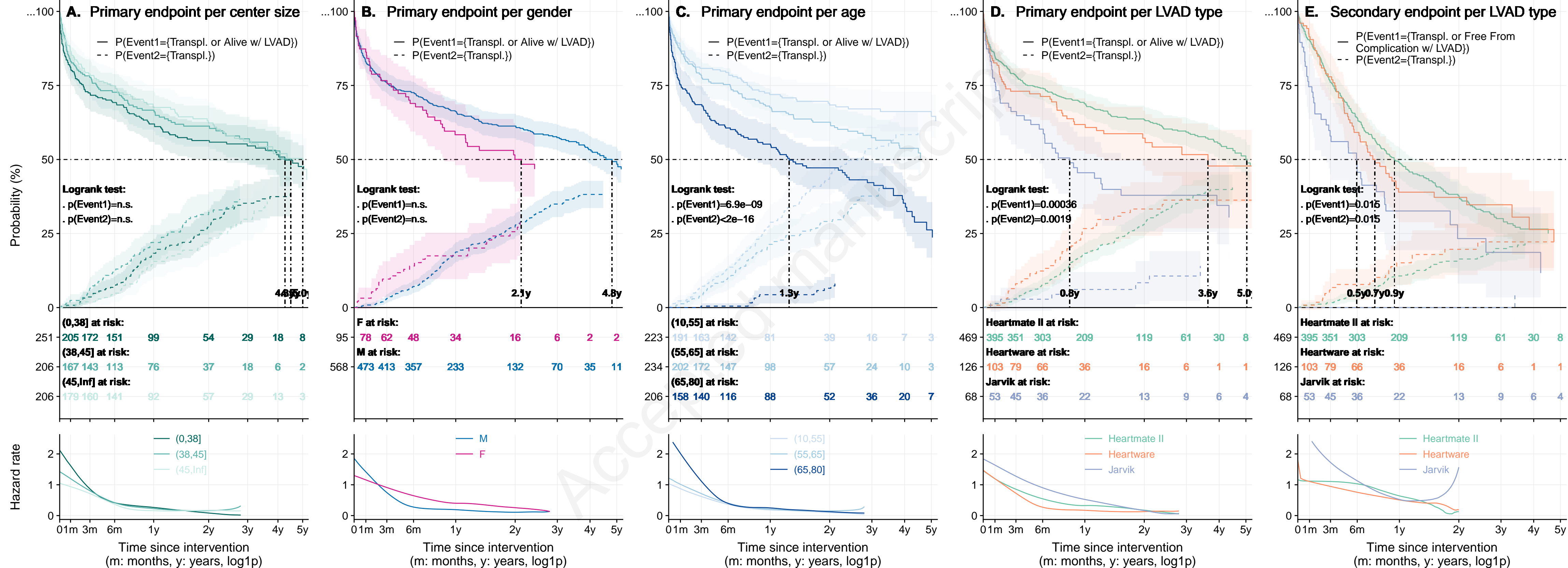
- 508 1. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA et al.
509 Second INTERMACS annual report: more than 1,000 primary left ventricular assist
510 device implants. *J Heart Lung Transplant.* 2010;29:1-10.
- 511 2. Estep JD, Starling RC, Horstmanshof DA, Milano CA, Selzman CH, Shah KB et al.
512 Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device
513 and Medical Management in Ambulatory Heart Failure Patients: Results From the
514 ROADMAP Study. *J Am Coll Cardiol.* 2015;66:1747-1761.
- 515 3. Mazzucotelli JP, Leprince P, Litzler PY, Vincentelli A, Le Guyader A, Kirsch M et al.
516 Results of mechanical circulatory support in France. *Eur J Cardiothorac Surg.*
517 2011;40:e112-7.
- 518 4. Finkelstein DM, Muzikansky A, Schoenfeld DA. Comparing Survival of a Sample to
519 That of a Standard Population. *J Natl Cancer Inst.* 2003;95:1434-9.
- 520 5. Galand V, Flécher E, Auffret V, Boulé S, Vincentelli A, Dambrin C et al. Predictors
521 and Clinical Impact of Late Ventricular Arrhythmias in Patients With Continuous-
522 Flow Left Ventricular Assist Devices. *JACC: Clinical Electrophysiology* 2018;4:1166-
523 75.
- 524 6. Cowger JA, Stulak JM, Shah P, Dardas TF, Pagani FD, Dunlay SM et al. Impact of
525 Center Left Ventricular Assist Device Volume on Outcomes After Implantation: An
526 INTERMACS Analysis. *JACC Heart Fail.* 2017;5:691-699.
- 527 7. Acharya D, Loyaga-Rendon R, Morgan CJ, Sands KA, Pamboukian SV, Rajapreyar
528 I et al. INTERMACS Analysis of Stroke During Support With Continuous-Flow Left
529 Ventricular Assist Devices: Risk Factors and Outcomes. *JACC Heart Fail.*
530 2017;5:703-711.

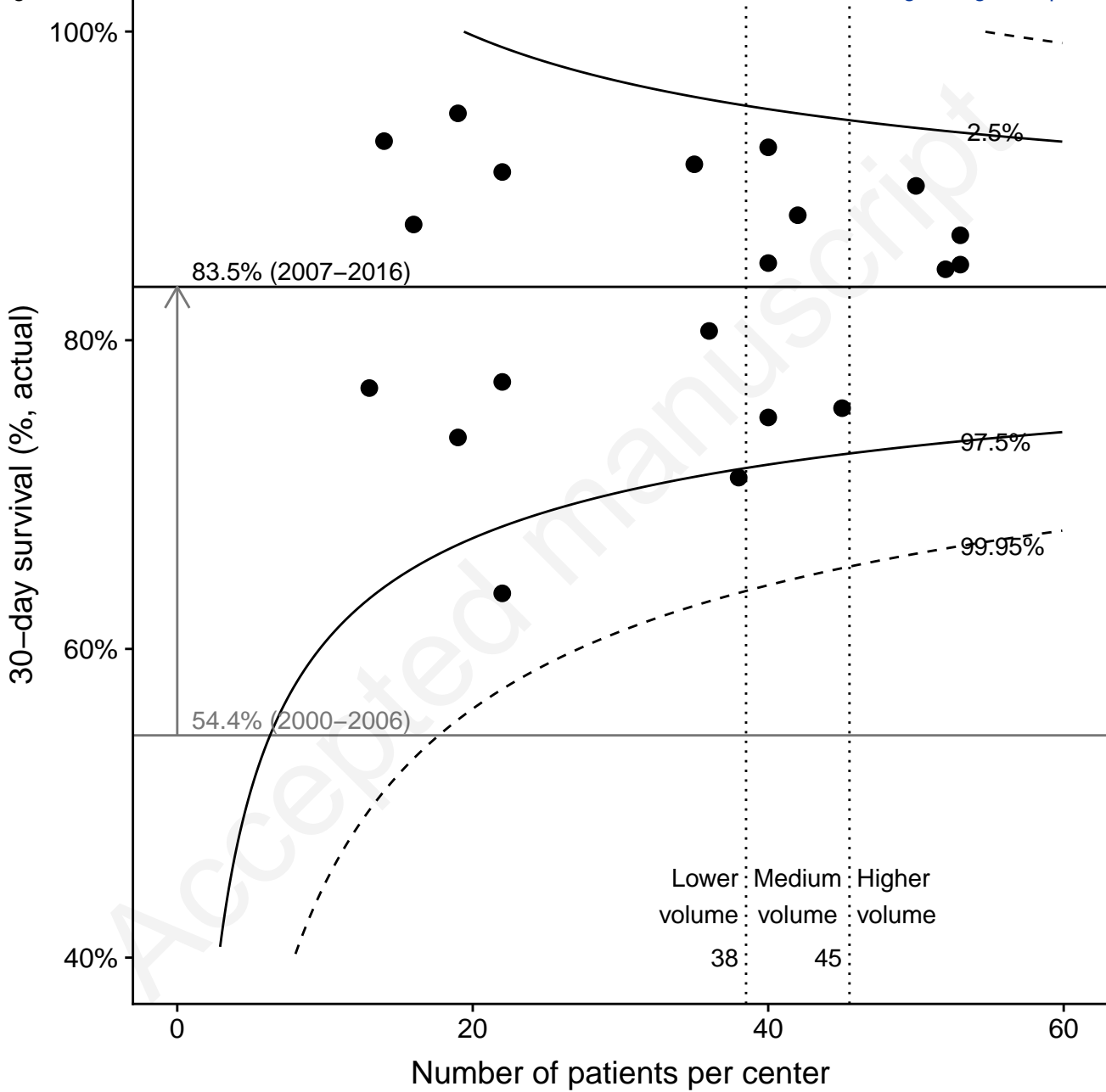
- 531 8. Maltais S, Kilic A, Nathan S, Keebler M, Emani S, Ransom J et al. PREVENTion of
532 HeartMate II Pump Thrombosis Through Clinical Management: The PREVENT
533 multi-center study. *J Heart Lung Transplant*. 2017;36:1-12.
- 534 9. Fukuhara S, Takeda K, Chiuzan C, Han J, Kurlansky PA, Takayama H et al.
535 Concomitant mitral repair and continuous-flow left ventricular assist devices: Is it
536 warranted? *J Thorac Cardiovasc Surg*. 2017;154:1303-1312.e4.
- 537 10. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL et al.
538 Eighth annual INTERMACS report: Special focus on framing the impact of adverse
539 events. *J Heart Lung Transplant*. 2017;36:1080-1086.
- 540 11. Flécher E, Anselmi A, Corbineau H, Langanay T, Verhoye JP, Félix C et al. Current
541 aspects of extracorporeal membrane oxygenation in a tertiary referral centre:
542 determinants of survival at follow-up. *Eur J Cardiothorac Surg*. 2014;46:665-71.
- 543 12. Hoefer D, Ruttman E, Poelzl G, Kilo J, Hoermann C, Margreiter R et al. Outcome
544 evaluation of the bridge-to-bridge concept in patients with cardiogenic shock. *Ann*
545 *Thorac Surg*. 2006;82:28-33.
- 546 13. Toda K, Fujita T, Seguchi O, Yanase M, Nakatani T. Role of percutaneous veno-
547 arterial extracorporeal membrane oxygenation as bridge to left ventricular assist
548 device. *J Artif Organs*. 2018;21:39-45.
- 549 14. Schibilsky D, Haller C, Lange B, Schibilsky B, Haeberle H, Seizer P et al.
550 Extracorporeal life support prior to left ventricular assist device implantation leads to
551 improvement of the patients INTERMACS levels and outcome. *PLoS One*.
552 2017;12:e0174262.
- 553 15. Agence de la Biomédecine. Procédures d'application des règles de répartition et
554 d'attribution des greffons prélevés sur personne décédée. MAJ dec 2013.
555 www.agence-biomedecine.fr

- 556 16.de By TMMH, Mohacsi P, Gahl B, Zittermann A, Krabatsch T, Gustafsson F et al.
557 The European Registry for Patients with Mechanical Circulatory Support
558 (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS):
559 second report. *Eur J Cardiothorac Surg.* 2017 in press. doi: 10.1093/ejcts/ezx320.
- 560 17.Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED et al.
561 Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung*
562 *Transplant.* 2015;34:1495-504.
- 563 18.Agence de la Biomédecine. Rapport activité greffe cœur 2016. [www.agence-](http://www.agence-biomedecine.fr)
564 [biomedecine.fr](http://www.agence-biomedecine.fr).
- 565 19.Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD et al.
566 The Registry of the International Society for Heart and Lung Transplantation:
567 Thirtieth Official Adult Heart Transplant Report--2013; focus theme: age. *J Heart*
568 *Lung Transplant.* 2013;32:951-64.
- 569 20.Axtell AL, Fiedler AG, Lewis G, Melnitchouk S, Tolis G, D'Alessandro DA et al.
570 Reoperative sternotomy is associated with increased early mortality after cardiac
571 transplantation. *Eur J Cardiothorac Surg.* 2019 in press. doi: 10.1093/ejcts/ezy443.
- 572 21.Seco M, Zhao DF, Byrom MJ, Wilson MK, Valley MP, Fraser JF et al. Long-term
573 prognosis and cost-effectiveness of left ventricular assist device as bridge to
574 transplantation: A systematic review. *Int J Cardiol.* 2017;235:22-32.
- 575 22.de By TM, Mohacsi P, Gummert J, Bushnaq H, Krabatsch T, Gustafsson F et al.
576 The European Registry for Patients with Mechanical Circulatory Support
577 (EUROMACS): first annual report. *Eur J Cardiothorac Surg.* 2015;47:770-6.
- 578 23.Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC et al. A
579 Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J*
580 *Med.* 2017;376:440-450.

- 581 24.Mehra MR, Goldstein DJ, Uriel N, Cleveland JC Jr, Yuzefpolskaya M, Salerno C et
582 al. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart
583 Failure. *N Engl J Med.* 2018;378:1386-1395.
- 584 25.Anselmi A, Flécher E, Corbineau H, Langanay T, Le Bouquin V, Bedossa M et al.
585 Survival and quality of life after extracorporeal life support for refractory cardiac
586 arrest: A case series. *J Thorac Cardiovasc Surg.* 2015;150:947-54.
- 587 26.Harvey L, Holley C, Roy SS, Eckman P, Cogswell R, Liao K et al. Stroke After Left
588 Ventricular Assist Device Implantation: Outcomes in the Continuous-Flow Era. *Ann*
589 *Thorac Surg.* 2015;100:535-41.
- 590 27.Stulak JM, Davis ME, Haglund N, Dunlay S, Cowger J, Shah P et al. Adverse
591 events in contemporary continuous-flow left ventricular assist devices: A multi-
592 institutional comparison shows significant differences. *J Thorac Cardiovasc Surg.*
593 *2016;151:177-89.*
- 594 28.Hanke JS, Dogan G, Zoch A, Ricklefs M, Wert L, Feldmann C et al. One-year
595 outcomes with the HeartMate 3 left ventricular assist device. *J Thorac Cardiovasc*
596 *Surg.* 2018;156:662-669.
- 597 29.Katz JN, Adamson RM, John R, Tatroles A, Sundareswaran K, Kallel F et al. Safety
598 of reduced anti-thrombotic strategies in HeartMate II patients: A one-year analysis
599 of the US-TRACE Study. *J Heart Lung Transplant.* 2015;34:1542-8.
- 600
601
602
603
604
605
606









Click here to access/download
Supplementary material
MARKED_4th REVISED.doc

