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RESEARCH ARTICLE

Clinical outcomes of temporary mechanical circulatory support as a direct bridge to heart transplantation: a nationwide Spanish registry

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Background In Spain, listing for high-urgent heart transplantation is allowed for critically ill candidates not weanable from temporary mechanical circulatory support (T-MCS). We sought to analyse the clinical outcomes of this strategy.

Methods and results We conducted a case-by-case, retrospective review of clinical records of 291 adult patients listed for high-urgent heart transplantation under temporary devices from 2010 to 2015 in 16 Spanish institutions. Survival after listing and adverse clinical events were studied. At the time of listing, 169 (58%) patients were supported on veno-arterial extracorporeal membrane oxygenation (VA-ECMO), 70 (24%) on temporary left ventricular assist devices (T-LVAD) and 52 (18%) on temporary biventricular assist devices (T-BiVAD). Seven patients transitioned from VA-ECMO to temporary ventricular assist devices while on the waiting list. Mean time on T-MCS was 13.1 ± 12.6 days. Mean time from listing to transplantation was 7.6 ± 8.5 days. Overall, 230 (79%) patients were transplanted and 54 (18.6%) died during MCS. In-hospital postoperative mortality after transplantation was 33.3%, 11.9% and 26.2% for patients bridged on VA-ECMO, T-LVAD and T-BiVAD, respectively ($P = 0.008$). Overall survival from listing to hospital discharge was 54.4%, 78.6% and 55.8%, respectively ($P = 0.002$). T-LVAD support was independently associated with a lower risk of death over the first year after listing (hazard ratio 0.52, 95% confidence interval 0.30–0.92). Patients treated with VA-ECMO showed the highest incidence rate of adverse clinical events associated with T-MCS.

Conclusion Temporary devices may be used to bridge critically ill candidates directly to heart transplantation in a setting of short waiting list times, as is the case of Spain. In our series, bridging with T-LVAD was associated with more favourable outcomes than bridging with T-BiVAD or VA-ECMO.

Keywords Ventricular assist device • Mechanical circulatory support • Heart transplantation • Extracorporeal membrane oxygenation

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Introduction

In recent years, shortage of donors and long waiting list times resulted in a progressive increase of the number of candidates who are bridged to heart transplantation (HT) under mechanical circulatory support (MCS), most of them by means of durable left ventricular assist devices (LVADs).[1,2]

Durable LVADs provide their best clinical outcomes when implanted in stable patients with isolated left ventricular failure. Survival after LVAD implantation slips early in patients requiring biventricular support, and in those operated in the course of acute decompensation.[2] Durable LVAD implantation is discouraged in patients with cardiogenic shock, who at a first step are more safely treated with temporary devices.[3]

Further management of patients recovering from cardiogenic shock under temporary MCS (T-MCS), otherwise considered suitable candidates for HT, remains a clinical challenge. Facing this situation, many teams would consider the transition from T-MCS to a durable LVAD as a bridge to HT; however, this 'double bridge' strategy has concerning results.[4] As an alternative option, an expedite pathway to high-urgent HT is enabled for such individuals in some countries.

Globally, the use of T-MCS as a direct bridge to HT is an unusual resort.[1] However, in Spain this is the most common mode of bridging.[5] Reasons for this particularity of our country are both tight economic restrictions on access to durable LVADs and quick availability of donors that allows such an approach. The experience of Spanish teams with the use of T-MCS as a direct bridge to HT gives a unique opportunity to deepen knowledge about the clinical results of this rather unusual strategy.

Methods

Setting

In Spain, the procurement and distribution of organ donors is coordinated by the Organización Nacional de Trasplantes (ONT), a public healthcare network that integrates all hospitals with capability for organ extraction or implantation around the country. In 2010, heart graft distribution criteria were modified,[6] and following that date the highest level of waiting list priority, the so-called '*ONT status 0*', is granted exclusively to HT candidates not weanable from T-MCS, or to those who develop complications related to durable ventricular assist devices (VADs)—infection, pump failure, or thrombosis. ONT status 0 confers priority over all other candidates nationwide to receive the first suitable donor heart available in the system—i.e. high-urgent HT.

Temporary devices[2] that qualify for ONT status 0 are those intended to provide full circulatory support for a maximum period of days or a few weeks, only at the in-hospital setting. Central or peripheral veno-arterial extracorporeal membrane oxygenation (VA-ECMO), percutaneous LVADs (e.g. Impella Recover®), and surgically implanted, extracorporeal continuous-flow VADs (e.g. Levitronix CentriMag®, Maquet Rotaflow®, Sorin Revolution®), or extracorporeal pulsatile-flow VADs (e.g. Abiomed AB 5000®, Abiomed BVS 5000®) meet these definition criteria. Devices intended for medium- or long-term, out-of-hospital circulatory support, either paracorporeal (e.g. BerlinHeart Excor®) or intracorporeal (e.g. HeartWare HVAD®, HeartMate II®) are considered as durable, so candidates listed on these modalities of MCS do not qualify as ONT status 0, unless in case of device-related complications. Intra-aortic balloon pump (IABP) is specifically excluded from the definition of T-MCS.

Study design

The ASIS-TC study (*'Empleo de los dispositivos de ASIStencia circulatoria mecánica de corta duración como puente a Trasplante Cardiaco urgente en España'*, in English *'Use of short-term mechanical circulatory support devices as a bridge to urgent heart transplantation in Spain'*) was a nationwide retrospective registry which included all patients listed for first, single-organ, high-urgent HT (ONT status 0) under T-MCS in Spain from 1 January 2010 to 31 December 2015. Patients aged <18 years, those listed for multi-organ transplantation or second HT, and those listed due to durable VAD-related complications were excluded.

Patients eligible for the registry were identified by means of the ONT database. A case-by-case retrospective review of medical records of all study subjects was conducted locally at every one of the 16 transplant centres of the country. Selected information regarding donors and post-transplant survival was extracted from the Spanish Heart Transplantation Registry.[5]

Pre- and post-transplant survival and adverse clinical events were analysed, both in the entire cohort and with regard to different modalities of T-MCS—temporary LVAD (T-LVAD), temporary biventricular assist device (T-BiVAD), or VA-ECMO. Definitions of study outcomes are detailed in the Supplementary material online, *Methods S1*.

The study protocol was approved by the Committee for Ethics in Clinical Investigation of the Autonomous Community of Galicia, Spain, and ratified by institutional review boards of participating hospitals.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as proportions. ANOVA and chi-square tests were used for statistical comparisons among groups, as required. The Clopper–Pearson exact method was used to estimate 95% confidence intervals (CI) of incidence rates of study outcomes.

One-year survival curves after high-urgent transplant listing were estimated by means of the Kaplan–Meier method and compared by means of the log-rank test. Independent predictors of 1-year survival after listing were identified by means of multivariable backward stepwise Cox regression analysis, choosing a "*P*-out" criterion of <0.05. Candidate variables selected for the model were those reflecting baseline clinical characteristics of patients at the time of listing that showed a statistically significant association with 1-year survival in univariable analyses. Statistical significance was set at $P < 0.05$ for all comparisons. Statistical analyses were performed with SPSS 20 (SPSS Inc., Chicago, IL, USA) and EpiDat 4.1.

Results

Patients and devices

During the study period, 291 patients were listed for high-urgent HT (ONT status 0) while on T-MCS in 16 Spanish institutions. At the time of listing, 169 (58%) patients were on VA-ECMO, 70 (24%) patients had a T-LVAD and 52 (18%) patients had a T-BiVAD. Before the instauration of T-MCS, 79 (27.1%) patients had been already listed for HT with a priority level inferior to status 0,

Table 1 Devices in place at the time of high-urgent listing

Devices	Patients, *n*
VA-ECMO	169 (58%)
Peripheral insertion, femoral artery[a]	144
Peripheral insertion, other artery[a]	17
Central insertion[b]	8
T-LVAD	70 (24%)
Levitronix CentriMag[b]	51
Impella Recover[a]	12
Abiomed BVS 5000[c]	6
Maquet Rotaflow[b]	1
T-BiVAD	52 (18%)
Levitronix CentriMag[b]	36
Abiomed BVS 5000[c]	14
Abiomed AB 5000[c]	1
Sorin Revolution[b]	1

T-BiVAD, temporary biventricular assist device; T-LVAD, temporary left ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
[a]Percutaneous, continuous-flow.
[b]Surgically implanted, continuous-flow.
[c]Surgically implanted, pulsatile-flow.

so they upgraded to the high-urgent level after the intervention. *Table 1* shows temporary devices in place at the time of high-urgent listing.

Seven patients listed on T-BiVADs and 5 patients listed on T-LVADs had been previously treated with VA-ECMO, but not listed while on it. Also, 2 patients listed on VA-ECMO have been previously treated with a T-LVAD, but not listed while on it. Before T-MCS instauration, 168 (58%) patients had an IABP, which remained in place at the time of high-urgent listing in 104 (35%) cases.

Table 2 shows the baseline clinical characteristics of the study patients at the time of high-urgent listing according to the modality of T-MCS. Patients on VA-ECMO more frequently presented with Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)[7] profile 1, more frequently had antecedents of open-chest surgery, and more frequently required ancillary vital supportive therapies like IABP and mechanical ventilation; this subgroup also showed the shortest time from device insertion to listing. The prevalence of active infection at listing was lower among VA-ECMO candidates.

Outcomes during temporary mechanical circulatory support

Mean duration of T-MCS was 13.1 ± 12.6 days (range 0–94 days), with significant differences among modalities of support (T-LVAD: 18.1 ± 15.9 days; T-BiVAD: 15.9 ± 15.8 days; VA-ECMO: 9.6 ± 8 days; $P < 0.001$). While awaiting transplantation, 7 patients listed initially on VA-ECMO transitioned to T-VADs—5 Levitronix CentriMag® BiVAD, 1 Levitronix CentriMag® LVAD, and 1 Maquet Rotaflow® LVAD.

Overall, 230 (79%) patients were transplanted while on T-MCS and 54 (18.6%) died before transplantation. Mean time from high-urgent listing to HT was 7.6 ± 8.5 days (range 0–81 days), varying significantly among modalities of support (T-LVAD: 8.3 ± 8.1 days; T-BiVAD: 10.5 ± 3.4 days; VA-ECMO: 6.5 ± 6.2 days; $P = 0.024$).

Rates of transplantation during support were 84.3%, 75% and 78.1% in patients listed on T-LVADs, T-BiVADs, and VA-ECMO, respectively ($P = 0.414$). Rates of death during support (before transplantation) were 11.4%, 25% and 19.5%, respectively ($P = 0.143$).

Only 7 (2.4%) patients were weaned from T-MCS. Of them, three were discharged after durable VAD implantation, one was discharged after elective HT, and three were discharged on medical therapy.

Figure 1 shows a flow chart of patients, devices and in-hospital outcomes in the study population. *Figure 2* shows a representation of competing outcomes of death on T-MCS, transplantation on T-MCS, or weaning from T-MCS over a 4-week period after listing.

Postoperative outcomes after transplantation

Table 3 shows donor characteristics and major in-hospital postoperative outcomes in 230 patients transplanted while on T-MCS. Cumulative rates of in-hospital post-transplant mortality were 33.3%, 26.2% and 11.9% in recipients bridged on VA-ECMO, T-BiVADs or T-LVADs, respectively ($P = 0.008$). No statistically significant differences among groups were observed with regard to other postoperative outcomes.

Overall 1-year outcomes after listing

In the whole cohort, 176 (60.5%) patients listed for high-urgent HT were discharged alive from hospital. Cumulative rates of survival from listing to hospital discharge in patients with T-LVADs, T-BiVADs and VA-ECMO were 78.6%, 55.8% and 54.4%, respectively ($P = 0.002$).

Figure 3 shows Kaplan–Meier survival curves over the first year after high-urgent listing of patients treated with different modalities of T-MCS (log-rank $P = 0.010$). In multivariable Cox regression, age, vasoactive-inotropic score,[8] serum lactate levels, active infection, and renal replacement therapy at the time of listing were independent predictors of mortality; isolated T-LVAD support was independently associated with higher survival. Univariable and multivariable Cox regression analyses are detailed in *Table 4*.

Adverse clinical events associated with temporary mechanical circulatory support

The overall incidence rate of adverse clinical events associated with T-MCS was 59 (95% CI 52–68) per 1000 devices-day (*Table 5*). In comparison to T-LVAD patients, VA-ECMO patients presented a statistically significant higher incidence rate of adverse clinical

Table 2 Clinical characteristics of the study patients at the time of high-urgent listing

Variables	T-LVAD ($n = 70$)	T-BiVAD ($n = 52$)	VA-ECMO ($n = 169$)	*P*-value
Clinical history				
Age (years)	52 ± 12	52 ± 10	50 ± 13	0.517
Female sex	22.9%	23.1%	24.3%	0.967
Body mass index (kg/m^2)	25 ± 4	26 ± 4	26 ± 5	0.313
Days from hospital admission to device insertion	10 ± 15	14 ± 22	12 ± 20	0.440
Days from device insertion to high-urgent listing	11 ± 14	7 ± 9	3 ± 5	<0.001
Patients in waiting list prior to device insertion	28.6%	23.1%	27.8%	0.948
Ischaemic heart disease	61.4%	44.2%	53.3%	0.168
Cardiogenic shock related to acute myocardial infarction	47.1%	25.0%	32%	0.023
Cardiogenic shock following cardiac surgery	4.3%	13.5%	10.1%	0.194
Diabetes mellitus	15.7%	23.1%	25.4%	0.262
Hypertension	24.3%	34.6%	33.1%	0.344
Hypercholesterolaemia	30%	36.5%	33.1%	0.748
Previous open-chest cardiac surgery	8.6%	15.4%	26.6%	0.004
History of malignancy	4.3%	5.8%	1.2%	0.139
Peripheral vascular disease	7.1%	1.9%	5.9%	0.427
Chronic obstructive pulmonary disease	14.3%	7.7%	4.1%	0.022
Previous stroke	4.3%	1.9%	7.1%	0.315
History of ventricular arrhythmia	25.7%	25%	27.2%	0.938
History of atrial fibrillation	15.7%	19.2%	22.5%	0.485
Previous cardiac arrest	14.3%	9.6%	17.2%	0.404
Implantable cardioverter-defibrillator	28.6%	23.1%	26%	0.791
Cardiac resynchronization therapy	8.6%	9.6%	11.8%	0.732
Active infection requiring i.v. therapy	18.6%	19.2%	6.5%	0.005
Clinical status				
INTERMACS profile				0.003
INTERMACS 1	24.3%	26.9%	42.6%	
INTERMACS 2	54.3%	50%	49.1%	
Other	21.4%	23.1%	8.3%	
Systolic blood pressure (mmHg)	98 ± 15	97 ± 9	102 ± 20	0.191
Heart rate (b.p.m.)	99 ± 17	89 ± 20	98 ± 22	0.027
Supportive therapies				
Intra-aortic balloon pump	21.4%	30.8%	43.2%	0.004
Renal replacement therapy	11.4%	11.5%	7.1%	0.435
Mechanical ventilation	38.6%	61.5%	77.5%	<0.001
Vasoactive-inotropic score (units)	27 ± 71	24 ± 76	43 ± 66	0.129
Laboratory				
Leucocytes (x10^9/L)	12.0 ± 5.1	11.8 ± 4.2	12.5 ± 5.5	0.576
Platelets (x10^9/L)	180 ± 103	183 ± 89	185 ± 81	0.893
INR	1.6 ± 0.7	1.3 ± 0.3	1.6 ± 0.8	0.321
Prothrombin time (s)	20 ± 13	17 ± 6	20 ± 10	0.593
Creatinine (mg/dL)	1.1 ± 0.9	1.3 ± 0.5	1.4 ± 0.8	0.051
Haemoglobin (g/dL)	9.5 ± 1.4	9.3 ± 1.4	10.5 ± 2	<0.001
Sodium (mEq/L)	138 ± 5	139 ± 6	139 ± 8	0.172
Bilirubin (mg/dL)	1.2 ± 1.1	1.6 ± 1.8	1.9 ± 2.3	0.057
Aspartate aminotransferase (IU/L)	92 ± 139	228 ± 482	302 ± 697	0.063
Alanine aminotransferase (IU/L)	78 ± 119	148 ± 279	318 ± 718	0.015
Albumin (g/dL)	3.0 ± 0.7	2.9 ± 0.6	3.0 ± 0.8	0.596
Arterial oxygen tension (mmHg)	110 ± 54	105 ± 37	117 ± 50	0.302
pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	0.171
Lactate (mmol/L)	1.6 ± 1.7	2.1 ± 2.3	2.4 ± 2.2	0.090
Echocardiography				
Left ventricular ejection fraction (%)	22 ± 9	25 ± 12	23 ± 13	0.358
Left ventricular end-systolic diameter (mm)	67 ± 12	62 ± 10	61 ± 13	0.049
Tricuspid annular plane systolic excursion (mm)	15 ± 4	15 ± 4	14 ± 5	0.136
Haemodynamics				
Cardiac index (mL/min/m^2)	2.4 ± 0.6	2.3 ± 0.7	2.1 ± 0.8	0.028
Central venous pressure (mmHg)	14 ± 5	12 ± 6	14 ± 6	0.316
Capillary wedge pressure (mmHg)	21 ± 8	21 ± 9	23 ± 9	0.450
Mean pulmonary pressure (mmHg)	26 ± 8	30 ± 15	30 ± 12	0.217
Transpulmonary gradient (mmHg)	8 ± 6	11 ± 8	8 ± 5	0.108

INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; T-BiVAD, temporary biventricular assist device; T-LVAD, temporary left ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

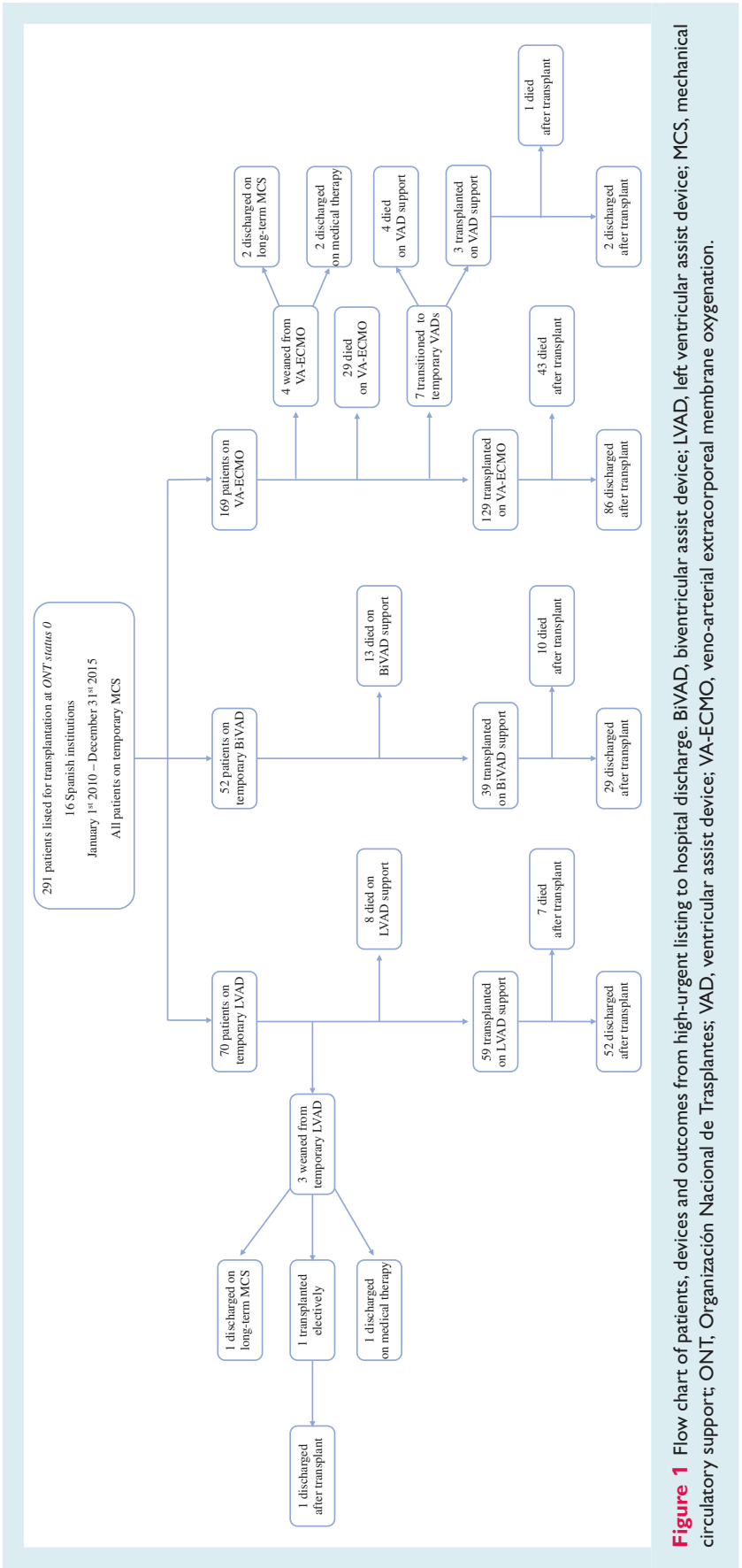

Figure 1 Flow chart of patients, devices and outcomes from high-urgent listing to hospital discharge. BiVAD, biventricular assist device; LVAD, left ventricular assist device; MCS, mechanical circulatory support; ONT, Organización Nacional de Trasplantes; VAD, ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

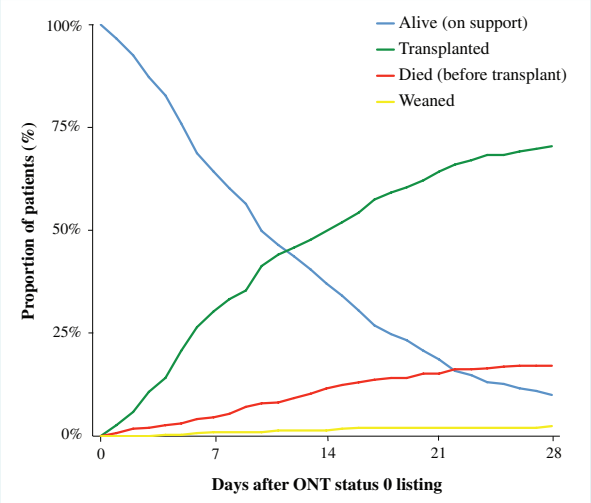

Figure 2 Depiction of the competing outcomes analysis for death, weaning or transplantation during a 28-day follow-up period after listing. At any given time point, the sum of the proportion of patients experiencing each outcome equals 100%. ONT, Organización Nacional de Trasplantes.

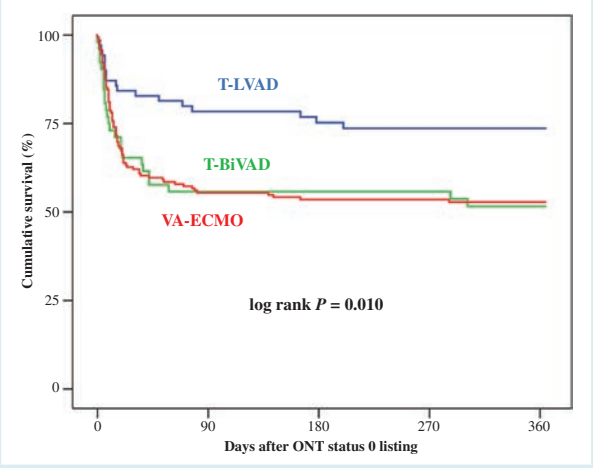

Figure 3 Kaplan–Meier depiction of survival over the first year after high-urgent listing, according to different modalities of circulatory support. ONT, Organización Nacional de Trasplantes; T-BiVAD, temporary biventricular assist device; T-LVAD, temporary left ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

events (71 vs. 47 events per 1000 devices-day, risk ratio 1.52, $P = 0.008$). The incidence rate of adverse clinical events among T-BiVAD patients was numerically, but not statistically significant, higher than among T-LVAD patients (57 vs. 47 events per 1000 devices-day, risk ratio 1.22, $P = 0.303$). Statistical comparisons of the individual incidence rates of all adverse clinical events among different modalities of T-MCS are presented in the Supplementary material online, *Table S1*.

The incidence rate of major adverse clinical events (device dysfunction, stroke, bleeding, or infection) was 50 (95% CI 43–58) per 1000 devices-day, without statistically significant differences among modalities of support (T-LVAD: 41 events per 1000 devices-day, T-BiVAD: 54 events per 1000 devices-day, VA-ECMO: 56 events per 1000 devices-day; $P > 0.005$ for all comparisons). Supplementary *Figure S1* shows the Kaplan–Meier depiction of survival free of major adverse clinical events in the study population.

Table 3 Donor characteristics and in-hospital postoperative outcomes after heart transplantation

	All patients ($n = 230$)	T-LVAD ($n = 59$)	T-BiVAD ($n = 42$)	VA-ECMO ($n = 129$)	*P*-value
Donor characteristics					
Female donor	59 (26%)	13 (22%)	11 (27%)	35 (26%)	0.756
Age (years)	42 ± 12	42 ± 13	43 ± 12	42 ± 11	0.958
Cold ischaemic time (min)	214 ± 60	213 ± 56	232 ± 46	209 ± 65	0.101
In-hospital postoperative outcomes					
Excessive surgical bleeding	72 (31%)	15 (25%)	18 (43%)	39 (30%)	0.163
Primary graft failure	75 (33%)	16 (27%)	17 (41%)	42 (33%)	0.369
Right ventricular failure	41 (18%)	7 (12%)	10 (24%)	24 (19%)	0.645
Left ventricular or biventricular failure	34 (15%)	9 (15%)	7 (17%)	18 (14%)	0.422
T-MCS after transplant	34 (15%)	7 (12%)	6 (14%)	21 (16%)	0.729
Open-chest redo surgery	40 (17%)	6 (10%)	10 (24%)	24 (19%)	0.176
Renal failure	64 (28%)	15 (25%)	15 (36%)	34 (26%)	0.447
Postoperative infection	121 (53%)	32 (54%)	23 (55%)	66 (51%)	0.883
In-hospital postoperative death	61 (26%)	7 (12%)	11 (26%)	43 (33%)	0.008
Days on ventilator after transplant	11 ± 17	8 ± 9	10 ± 14	13 ± 21	0.196
Days of ICU stay after transplant	18 ± 18	16 ± 22	20 ± 19	18 ± 19	0.725
Days of hospital stay after transplant	38 ± 37	36 ± 29	39 ± 34	38 ± 40	0.930

ICU, intensive care unit; T-BiVAD, temporary biventricular assist device; T-LVAD, temporary left ventricular assist device; T-MCS, temporary mechanical circulatory support; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Table 4 Clinical predictors of 1-year all-cause mortality: univariable and multivariable Cox proportional hazards regression

	Univariable analysis			Multivariable analysis		
	Unadjusted HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Age (per 10 years)	1.21	1.03–1.42	0.023	1.29	1.06–1.56	0.010
Vasoactive-inotropic score (per 10 units)	1.03	1.06–1.09	<0.001	1.07	1.04–1.10	<0.001
Creatinine (mg/dL)	1.33	1.10–1.60	0.004	–	–	–
Lactate (mmol/L)	1.11	1.03–1.21	0.009	1.10	1.00–1.20	0.049
Renal replacement therapy	2.22	1.35–3.67	<0.001	2.02	1.06–3.84	0.032
Isolated LVAD support	0.47	0.29–0.78	0.003	0.52	0.30–0.92	0.025
Mechanical ventilation	1.67	1.12–2.49	0.012	–	–	–
Intra-aortic balloon pump	1.48	1.03–2.12	0.033	–	–	–
Active infection requiring i.v. therapy	1.74	1.08–2.02	0.023	2.13	1.20–2.79	0.010
INTERMACS profile 1	2.03	1.42–2.90	<0.001	–	–	–

CI, confidence interval; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.

Patients who experienced major adverse clinical events associated with T-MCS showed lower rates of transplantation (71.7% vs. 92.3%, $P < 0.001$), higher rates of death during support (25.1% vs. 6.7%, $P < 0.001$), lower survival from listing to hospital discharge (55.1% vs. 70.2%, $P = 0.012$) and lower 1-year survival after listing (52.5% vs. 66.5%, log-rank $P = 0.011$; see Supplementary material online, *Figure S2*) than patients who did not.

Discussion

In this 16-institution study, we analysed the clinical outcomes of 291 Spanish patients who were listed for high-urgent HT while on T-MCS during the period 2010–2015. In a setting of short waiting times, overall survival from listing to hospital discharge was 61% and overall 1-year survival after listing was 58%. Patients bridged on T-LVADs presented better outcomes than patients bridged on VA-ECMO or T-BiVADs. Adverse clinical events associated with T-MCS were frequent in the study population.

In our registry, the strategy of bridging patients directly to high-urgent HT was associated with significant short-term mortality, divided almost half-and-half between the waiting list period and the early post-transplant period. Nevertheless, these results must be put in the context of the critically ill population treated. The majority of our patients showed INTERMACS profiles[7] 1 or 2, with signs of profound haemodynamic compromise and end-organ dysfunction, and frequently required ancillary supportive therapies like mechanical ventilation, high-dose vasoactive drugs, or IABP. In the absence of other efficient therapeutic alternatives, we feel that these clinical results are in general terms acceptable, even though they could be refined. However, it should be recognized that these results were obtained by treating a selected population of young HT candidates (mean age 51 years), with a relatively low prevalence of pre-existing adverse co-morbidities, in the context of a reasonable availability of organ donors. This strategy might not be valid in other settings.

It might be argued that durable VAD implantation as a bridge to HT constitutes a better option than primary listing in candidates depending on T-MCS. However, published experience with this 'double-bridge' strategy is limited, and with concerning results. Two small American studies,[5,9] conducted in 68 and 45 patients, respectively, who underwent HeartMate II® or HeartWare HVAD® implantation while on T-MCS, reported consistent 1-year postoperative survival rates of 70%. In another single-centre European cohort of 20 patients who transitioned from ECMO to Berlin Heart Excor®, 1-year postoperative survival was reduced to 40%.[10] Some concern has been generated about a potential negative impact of preoperative long-term MCS on post-transplant survival;[11] however, post-transplant outcomes of successfully bridged patients were not analysed in these studies.[5,9,10]

Mean waiting time for transplantation was short in our series (7.6 days), allowing that near 80% patients listed on T-MCS received a graft. These figures reflect the efficient performance of the 'ONT status 0' protocol, comparable to UNOS status 1A,[12] and superior to Eurotransplant high-urgency.[13] Details about the organization and functioning of our national organ donor-sharing network have been described previously.[14]

Clinical complications associated with T-MCS were common in our population. The overall incidence rate of adverse events was near 6% per patient and day on support; daily risks of infection and serious bleeding were around 3%, while daily risks of stroke and device dysfunction exceeded 0.5%. Vascular access site complications requiring local intervention were frequent in patients with percutaneous devices; renal replacement therapy and open-chest redo surgery were also occasionally needed. Even despite a liberal use of concomitant IABP support,[15] daily rates of acute pulmonary oedema were as higher as 1.5% in patients treated with VA-ECMO. Incidence rates of adverse events were consistent with those described in other registries,[16,17] and substantially higher than those reported in patients with durable devices.[2] Not surprisingly, complications associated with T-MCS had a significant

Table 5 Incidence rates of clinical complications associated with temporary mechanical circulatory support, expressed as number of subjects having an event per 1000 device-days on support

	All devices ($n = 298$)		T-LVAD ($n = 72$)		T-BiVAD ($n = 57$)		VA-ECMO ($n = 169$)	
	N	Rate (95% CI)	*N*	Rate (95% CI)	*N*	Rate (95% CI)	*N*	Rate (95% CI)
Infection	120	32 (26–38)	36	28 (19–38)	32	36 (25–52)	52	32 (24–42)
Bleeding	118	31 (26–37)	32	25 (17–35)	29	33 (22–47)	57	35 (27–45)
Vascular access site complication[a]	41	26 (18–35)	4	59 (52–68)	–	–	37	24 (17–34)
Venous thromboembolism	6	2 (1–3)	0	0	0	0	6	4 (1–8)
Non-CNS arterial thromboembolism	15	4 (2–6)	0	0	5	6 (2–13)	10	6 (3–11)
Stroke	23	6 (4–9)	9	7 (3–13)	6	7 (3–15)	8	5 (2–10)
Renal failure	59	16 (12–20)	18	14 (8–22)	13	15 (8–25)	28	17 (11–25)
Open-chest redo surgery[b]	40	18 (13–25)	21	17 (11–26)	18	21 (12–32)	1	9 (0–52)
Pleural effusion	31	8 (6–12)	6	5 (2–10)	16	18 (10–30)	9	6 (3–11)
Pneumothorax	6	2 (1–3)	3	2 (0–6)	1	1 (0–6)	2	1 (0–4)
Pericardial effusion	26	7 (5–10)	10	8 (4–14)	7	8 (3–16)	9	6 (3–11)
Cardiac tamponade	20	5 (3–8)	9	7 (3–13)	5	6 (2–13)	6	4 (1–8)
Wound dehiscence[b]	4	2 (0–5)	2	1 (0–5)	2	2 (0–8)	0	0
Right ventricular failure[c]	9	7 (3–13)	9	7 (3–13)	–	–	–	–
Acute pulmonary oedema[d]	25	15 (10–23)	–	–	–	–	25	15 (10–23)
Haemolysis	20	5 (3–8)	7	5 (2–11)	4	5 (1–12)	9	6 (3–11)
Device dysfunction	25	7 (4–10)	9	7 (3–13)	5	6 (2–13)	11	7 (3–12)
Device exchange or replacement	21	6 (3–8)	8	6 (3–12)	4	5 (1–12)	9	6 (3–11)
Major adverse clinical events[e]	191	50 (43–58)	53	41 (30–53)	47	54 (40–71)	91	56 (45–69)
All adverse clinical events	226	59 (52–68)	61	47 (36–60)	50	57 (42–75)	115	71 (58–85)

CI, confidence interval; CNS, central nervous system; T-BiVAD, temporary biventricular assist device; T-LVAD, temporary left ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
[a]Rates calculated only for percutaneous LVADs ($n = 12$) and peripheral VA-ECMO ($n = 161$).
[b]Rates calculated only for surgically implanted LVADs ($n = 60$), surgically implanted BiVADs ($n = 57$), and central VA-ECMO ($n = 8$).
[c]Rates calculated only for LVADs ($n = 72$).
[d]Rates calculated only for VA-ECMO ($n = 169$).
[e]Device dysfunction, infection, bleeding, or stroke.

impact on the chance of getting an organ and, subsequently, on survival.

We observed relevant differences in clinical outcomes according to the modality of T-MCS selected for bridging. Patients listed on T-LVADs showed significant higher survival rates than those listed on T-BiVADs or VA-ECMO. Patients of these two latter groups had higher rates of complications associated with T-MCS while awaiting transplantation; however, survival differences were driven mainly by an excess of early post-transplant mortality, similarly to results reported previously.[18–20] Patients bridged on T-LVADs showed comparable outcomes to those of medically managed patients who undergo elective HT in our country.[5] A glance to baseline clinical characteristics reveals that the T-LVAD group represented a less sick population than the rest of the cohort, a fact that probably has conditioned these results.

Interestingly, patients supported with VA-ECMO showed the shortest time since device implantation to listing and, subsequently, to HT. This finding is a clear reflection of how the presumed durability of the device selected for bridging impacts the timing of clinical decisions in critically ill HT candidates. It is probable, indeed, that some VA-ECMO patients were listed, and then transplanted, 'too early', even before complete recovery of end-organ function could be achieved. In the other hand, complications associated with prolonged VA-ECMO support, such as insufficient left ventricular unloading, pulmonary distress, or coagulopathy, may have jeopardized post-transplant outcomes in candidates who did not get an organ during the first days after being stabilized.

Our study has a few limitations. As a retrospective, observational investigation, it is exposed to potential selection, information, and confusion biases. The study involved a wide variety of institutions across Spain, with different centre-specific protocols, volume of activity and clinical experience. Adverse clinical events were self-reported by local investigators, without external monitoring; in some cases, this might lead to underestimation of their incidence. Also, the limited number of patients analysed may have prevented us to demonstrate as statistically significant some clinically relevant results; in particular, this fact may have affected the comparison of outcomes of patients bridged on different modalities of T-MCS. Finally, our results may not apply to other networks with longer waiting times for high-urgent HT and higher availability of long-term MCS devices than the Spanish one.

In conclusion, the Spanish experience shows that the use of T-MCS as a direct bridge to high-urgent HT is a feasible therapeutic strategy in the context of an efficient donor allocation system that ensures availability of a suitable graft for the patient within a few days after listing. In our cohort, patients listed for HT

under T-LVADs showed comparable outcomes to those reported previously for medically managed candidates transplanted in our country. A higher incidence of associated adverse clinical events and mortality was observed among candidates listed on T-BiVADs or VA-ECMO; nevertheless, clinical outcomes of these critically ill individuals were, in general lines, acceptable, and similar to those reported from other networks. Our observation, however, might not be extensible to other countries with longer waiting list times for transplantation. Further investigation is warranted to clarify which is the best therapeutic option for the management of critically ill HT candidates dependent on T-MCS.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Methods S1. Definition of variables.

Table S1. Risk ratios of individual adverse clinical events associated with mechanical circulatory support among different types of devices.

Figure S1. Survival free of major adverse clinical events associated with temporary mechanical circulatory support (device dysfunction, bleeding, stroke, or infection): Kaplan–Meier analysis.

Figure S2. Kaplan–Meier survival curves over the first year after high-urgent transplant listing in patients who developed major adverse clinical events (ACE) associated with temporary mechanical circulatory support, as compared with those who did not.

Appendix S1. Participating hospitals, collaborators and recruited patients.

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