

# Initial 3-year outcomes with left ventricular assist devices in a country with a nascent heart transplantation program

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## Abstract

**Aims** The need for the left ventricular assist devices (LVAD) in patients with end-stage heart failure is well established, but prior to 2011, this was not available to patients in Kazakhstan. We describe the development of the sole LVAD programme in the context of a nascent heart transplantation programme and clinical outcomes for the first three years.

**Methods and results** From November 2011 to November 2014, 146 patients underwent implantation of 152 VADs (approximately 50 devices implanted per year). We retrospectively analyzed data from 135 LVAD patients who received HeartMate II ( $n=95$ ) or HeartWare ( $n=40$ ) devices. In 75 patients LVAD was used as a bridge-to-transplantation and in 60 patients as destination therapy, but only 3 of 135 LVAD patients received heart transplant. Forty-three patients of the LVAD cohort had died by the end of the follow-up period. The mean time on LVAD was  $466 \pm 330$  days (range 5–1200 days). Kaplan–Meier survival estimates for patients who continued on LVAD support were 93% after 1 month, 86% after 6 months and 77% after 12 months. The most common complications within the first 30 days after implant included right ventricular failure ( $n=20$ , 1.85 events/patient-year), renal failure ( $n=19$ , 1.76 events/patient-year) and bleeding ( $n=33$ , 3.0 events/patient-year). Beyond 30 days adverse events included driveline infections ( $n=46$ , 0.56 events/patient-year) and stroke ( $n=33$ , 0.21 events/patient-year).

**Conclusions** LVADs are an important therapeutic alternative to heart transplantation in the context of a developing heart transplant programme with outcomes that are comparable to those reported by other centres.

**Keywords** Left ventricular assist device; Mechanical circulatory support; Heart failure; Kazakhstan; Heart transplantation

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## Introduction

Durable left ventricular assist devices (LVADs) improve the quality and length of life by restoring normal circulation in the majority of recipients.<sup>1</sup> Since the introduction of smaller and more durable continuous-flow LVADs, there has been a steady decline in adverse event rates and, consequently, better survival rates.<sup>2–4</sup> Recent studies have shown that the 1-year survival for bridge to transplant (BTT) is 85%, and the 2-year survival for destination therapy (DT) is 76%. Measures for quality of life and functional status have also

demonstrated substantial benefit from LVAD support in patients with severe debilitation secondary to heart failure.<sup>5</sup> While several clinical studies have confirmed that LVAD support provides considerable benefits for the majority of recipients, this therapy remains seriously underutilized.<sup>6</sup>

In 1958, surgeons performed the first open-heart surgery in Kazakhstan. The discipline developed slowly, with approximately 200 surgeries performed each year. Since gaining independence in 1991, 26 cardiac surgery centres were established across the country, and in 2014, there were more than 8000 cardiac surgeries performed in Kazakhstan. Prior to

2011, there was no VAD programme and most patients could not afford to travel outside the country for treatment; patients with severe heart failure received medical treatment that helped palliate the disease with limited impact on long-term outcomes. In this context, the National Research Center for Cardiac Surgery (NRCCS), located in Astana, Kazakhstan, established a mechanical circulatory support programme in 2011. With the help of experienced European centres, the NRCCS established the sole VAD programme in Kazakhstan providing VAD support to all regions of this, the world's ninth largest country. This report describes the logistics and clinical results for the first three years of the programme.

## Methods

This was a retrospective, observational study of patients who received LVAD implantation from the start of the programme in November 2011 to November 2014 and the last date of follow up was 28 February 2015. The NRCCSVAD team uses four devices—the HeartMate II and CentriMag VAD (Thoratec Corporation, Pleasanton, CA, USA), HeartWare HVAD (HeartWare International, Framingham MA, USA) and the HeartMate III (Thoratec), the latter of which was approved for use in BTT and DT in Kazakhstan in 2014. Our analysis included all patients with end-stage heart failure who received a VAD and excluded the small number of patients who received HeartMate III devices. We used the adverse event definitions as described by the INTERMACS group.<sup>7</sup> The investigation conforms with the principles outlined in the Declaration of Helsinki. Local ethics committee approval was obtained, and all patients gave written consent agreeing that their clinical data could be used for research purposes.

## Statistical analysis

Descriptive analysis was performed by presenting the mean  $\pm$  SD for continuous data. Outcome measures used were all-cause mortality using Kaplan–Meier survival curves. Subgroup analyses were performed on INTERMACS classification at baseline and year of programme. Statistical analyses were performed using SPSS Statistics version 22.

## Programme

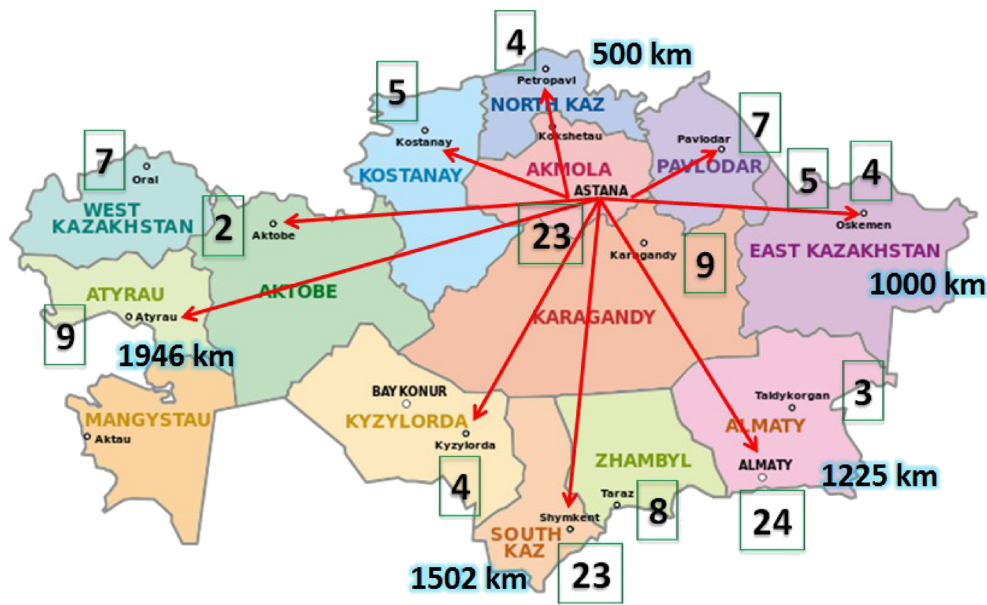
Kazakhstan is a country with 17 million residents dispersed over 2.7 million km<sup>2</sup> (6.4 persons/km<sup>2</sup>). In 2010, the NRCCS initiated plans to establish an advanced heart failure care programme. Initial resources available at the time included a state-of-the-art cardiac surgery hospital that opened in October 2011, an experienced surgical team and financial support from the Kazakhstan Ministry of Health. Surgical training was provided by the manufacturers of the VAD

devices. NRCCS staff also received training at centres in the Czech Republic, Lithuania, United States and Germany. A multidisciplinary team was established to cover all the responsibilities related to selection of patients and continued care, both within the city of Astana and in remote regions across the country (*Figure 1*). The team developed mechanical circulatory support operating procedures and provided training to staff from 15 regional hospitals and clinics across the country.

Distances from the NRCCS to the regional centres are up to 2000 km. Because patients are discharged home to regions distant from the NRCCS, identification of a cardiologist knowledgeable in VAD is essential. Cardiologists ( $n=31$ ), surgeons ( $n=8$ ) and nurses ( $n=12$ ) participated in educational meetings at the NRCCS that were designed to provide sufficient knowledge of the VAD systems to enable first-line-of-care in cases of emergency and routine follow-up assessment. Annual retraining is provided. Cardiologists who work far from a tertiary care centre are given 2 days of training. Patients and their family are also trained on the VAD system prior to patient discharge. Training consists of heart failure medical management, including anticoagulation therapy, monitoring for complications (e.g. driveline infections and stroke) and directions related to device troubleshooting. The programme provides air ambulance transport when necessary to return the patient to Astana via chartered plane or helicopter for advanced evaluation and care. Reasons for this can include device troubleshooting, pump thrombosis, stroke, major bleeding and generalized infections. If patients are not sufficiently stable for transport, we provide advice to local physicians on patient management.

Patients with advanced heart failure are referred to NRCCS for consideration of an implantable VAD; referrals come from within the institution and from cardiologists around Kazakhstan (*Figure 1*). A multidisciplinary team approach is used for patient selection and continued care. The team includes VAD surgeons, cardiologists, a VAD coordinator, anaesthesiologists, neurologists, nephrologists, nurses, a dietician, psychologists, a pharmacist and physiotherapists. Pre-implant psychological assessment and evaluation of social support, including obtaining information about the patient's home environment to ensure essential VAD operating and management conditions, are conducted before implant. The indication for LVAD support according to usual international criteria for BTT or DT is determined during the workup phase. The heart transplant programme in Kazakhstan is in a nascent stage, and therefore, patients that are determined to be BTT are expected to have an extended duration of LVAD support. In the three years prior to February 2015, 14 heart transplant surgeries have been performed in Kazakhstan—13 at the NRCCS in Astana and 1 in the city of Almaty. After the assessment, LVAD candidates are educated about the surgery, follow-up care, and self-care requirements; then, signed informed consent is obtained. There are no specific criteria for device selection (e.g. HeartMate II vs. HeartWare HVAD)

**Figure 1** Kazakhstan: Number of VAD patients of region of residence and driving distances from NRCCS.



Source: Map of Kazakhstan is from <https://en.wikipedia.org/wiki/Kazakhstan> and freely available under the Creative Commons Attribution-ShareAlike License ([https://en.wikipedia.org/wiki/Wikipedia:Text\\_of\\_Creative\\_Commons\\_Attribution-ShareAlike\\_3.0\\_Unported\\_License](https://en.wikipedia.org/wiki/Wikipedia:Text_of_Creative_Commons_Attribution-ShareAlike_3.0_Unported_License)).

except that the HVAD device is often preferred in the case of smaller patients (body surface area 1.2–1.5 m<sup>2</sup>).

Implantation techniques and postoperative management followed established guidelines.<sup>8–9</sup> Anticoagulation therapy for HeartMate II patients included an early, postoperative intravenous infusion of heparin and then, when possible, daily oral aspirin (100 mg) and warfarin regimen, with a target international normalized ratio (INR) of 2.0–2.5. There are some differences in anticoagulation strategy for HVAD patients compared with LVAD patients—HVAD patients are given a higher aspirin dose (300 mg daily) and higher warfarin dose—to reach an INR range of 2.5–3.5.

After patients are stabilized, they are transferred from the intensive care unit to the cardiac surgery ward and then to the LVAD department for rehabilitation and preparation for hospital discharge. Detailed self-care instruction is provided to patients and their family members; for patients who will return to their home outside of Astana, any necessary instruction is provided to medical professionals in that community for continued care. Several patients who previously received implants have subsequently joined NRCCS staff in various roles and at times provide emotional support to new patients during their hospital stay. Patients and family members provide all VAD-related care and maintenance. In each community with two or more patients, a support group has been formed to assist other patients with social adaptation. Each patient carries an identification card that has their name, a description of the device, serial number and contact information for the VAD coordinator in Astana. Patient and

caregivers are trained on proper driveline care, which is performed daily in summertime and 3 times per week in the winter. After discharge, local physicians see patients monthly for 3 months, then every 3 months or more often as needed. All patients return to the NRCCS in Astana at months 1, 3 for laboratory analysis and echocardiography and at month 6 for catheterization, laboratory analysis and spirometry. While at home, patients maintain contact with the NRCCS VAD coordinator and nurses. Patients communicate health status, driveline status, weekly INR results directly to the VAD coordinator and nurses using Whatsapp, a software application for mobile phone devices. Patients take photos of their driveline exit site and send these once weekly to the VAD coordinator and nurses. If necessary, the NRCCS surgeons are asked to assess the patient.

## Results

From November 2011 to November 2014, 146 patients underwent implantation of 152 VADs at NRCCS (approximately 50 devices implanted per year). Excluding HeartMate III devices, 138 patients were implanted with 144 VADs. A total of 135 patients received a device for left ventricular assist, and of these, 95 patients (65%) received a HeartMate II device and 40 patients (26%) received a HeartWare device for left ventricular assist. Two patients received BiVADs, and one received total artificial heart using two pumps. Three patients underwent reimplantation of original LVAD because of pump thrombosis.

The patients were 83% male and had an average age of 50 years (Table 1). Three children aged 11, 16 and 16 years received LVADs, and all other patients were over 18 years of age. Children are not eligible to be heart donors in Kazakhstan under current laws; therefore, we rarely perform VAD implantation in children because of the low possibility of appropriate adult heart donors that are available. Half of the patients had heart failure with ischemic aetiology. Severely ill patients with INTERMACS profiles 1 or 2 comprised 23% of our study population. A slight majority of our patients received the implant as a BTT.

By the end of the follow-up period, 43/135(32%) LVAD patients had died. The other 92 patients either received a transplant ( $n=3$ ), had the device turned off without explantation

( $n=2$ ) or remained alive with ongoing LVAD support at the end of the follow up period ( $n=87$ ). The median time from the LVAD implantation to heart transplantation was  $329 \pm 137$  days (range 202–475 days). No patients underwent explantation other than the patients receiving heart transplant. The two patients, whose pumps were turned off because of thrombosis, were in stable condition and waiting for heart transplant at the time this manuscript was written. Following implant surgery the mean time in the intensive care unit was  $6.8 \pm 8.7$  days and the mean duration of hospital stay from the LVAD implant day to the day of discharge was  $32.3 \pm 14.0$  days.

The mean time on the device for left ventricular assist was  $466 \pm 330$  days (range 5–1200 days).

Kaplan–Meier survival estimates for all patients who continued on LVAD support were 93% after 1 month, 86% after 6 months and 77% after 12 months (Figure 2). Survival rates by baseline INTERMACS profile showed that patients with more severe illness had lower survival rates after 12 months, compared with patients with less severe illness (Figure 3). When we compared survival rates by year of the programme after 12 months of VAD support, patients implanted in year one had a survival of 70%, whereas patients implanted in year two or year three had 12-month survival rates of 81 and 83% respectively (Figure 4). The mean (SD) 6-min walk distance before LVAD implantation was  $166 \pm 96$  m, and after 3 months was  $395 \pm 73$  m ( $P < 0.001$ ).

**Table 1** Baseline characteristics and concomitant procedures for patients implanted with a VAD ( $n = 138$ )

Characteristics of patients	$n$ (%) or mean $\pm$ SD (range)
Age, year	$50.5 \pm 13.5$ (11–76)
Gender, male/female	121 (87.7)/17 (12.3)
BSA, m <sup>2</sup>	$1.85 \pm 0.21$
Diagnosis, cardiomyopathy	
Ischemic	69 (50)
Dilated	52 (37.68)
Valvular	9 (6.52)
Hypertensive	6 (4.35)
Hypertrophic	2 (1.45)
ICD prior to VAD implantation	12 (8.7)
CRT-D prior to VAD implantation	10 (7.25)
Indication	
BTT	77 (55.8)
DT	61 (44.2)
INTERMACS profile	
1	7 (5.07)
2	16 (11.6)
3	32 (23.19)
4	75 (54.34)
5	8 (5.8)
NYHA functional class	
3	73 (52.9)
4	65 (47.1)
LV ejection fraction, %	$22.38 \pm 5.8$
TAPSE, cm	$1.38 \pm 0.32$
Cardiac index, l/min/m <sup>2</sup>	$1.77 \pm 0.5$
Concomitant procedure	
CABG	21 (15)
AV replacement	13 (9.4)
TV repair	10 (7.3)
MV repair/replacement	3 (2.2)/2 (1.5)
Closure of the left atrial appendage	21 (15.22)
RFA	4 (3)
Other (thrombectomy from the LV, LA etc.)	14 (10.1)

Abbreviations: aortic valve; AV, body surface area; bridge to transplant; BSA, BTT, CABG, cardiac resynchronization therapy device with defibrillator function; coronary artery bypass grafting; CRT-D, destination therapy; DT, ICD, implantable cardioverter-defibrillator; Interagency Registry for Mechanically Assisted Circulatory Support; INTERMACS, LA, left atrium; left ventricle; LV, mitral valve; MV, New York Heart Association; NYHA, TAPSE, tricuspid annular plane systolic excursion; tricuspid valve; TV, radiofrequency ablation RFA.

## Adverse events

The most common complication during the first 30 days was bleeding requiring reoperation [ $n=10$  (7%)] or RBC transfusion [ $n=23$  (17%)] (Table 2). Right ventricular failure was observed in 20 (15%) patients during the first 30 days. In one case, a patient (male, 48 years) after implantation of LVAD HeartMate II was required the setting of the RVAD Levitronix Centrimag to support the right ventricle. He was on RVAD for 147 days, followed by HeartWare implantation for the right ventricle long-term support. Six months after the first surgery, the patient was discharged home. During the first 30 days renal failure requiring hemodialysis occurred in 19 (14%) patients who did not require this procedure prior to implant. Ventricular arrhythmias occurred in 10 (7%) patients, and 6 (4.4%) of them developed during the first 30 days after implantation. Two patients required implantation of a cardioverter defibrillator (ICD) 10 and 32 months after LVAD implantation. One patient experienced a psychotic episode during the first 30 days during which he purposely damaged the driveline but it did not affect the pump function.

After the first 30 days, the most common adverse event was driveline infection occurring in 46 (34%) patients and of these, 13 (10%) underwent surgical debridement. Stroke occurred in 33 (24%) patients including 18 (13%) patients with ischemic stroke and 15 (11%) patients with hemorrhagic

Figure 2 Kaplan–Meier analysis: Survival for LVAD patients.

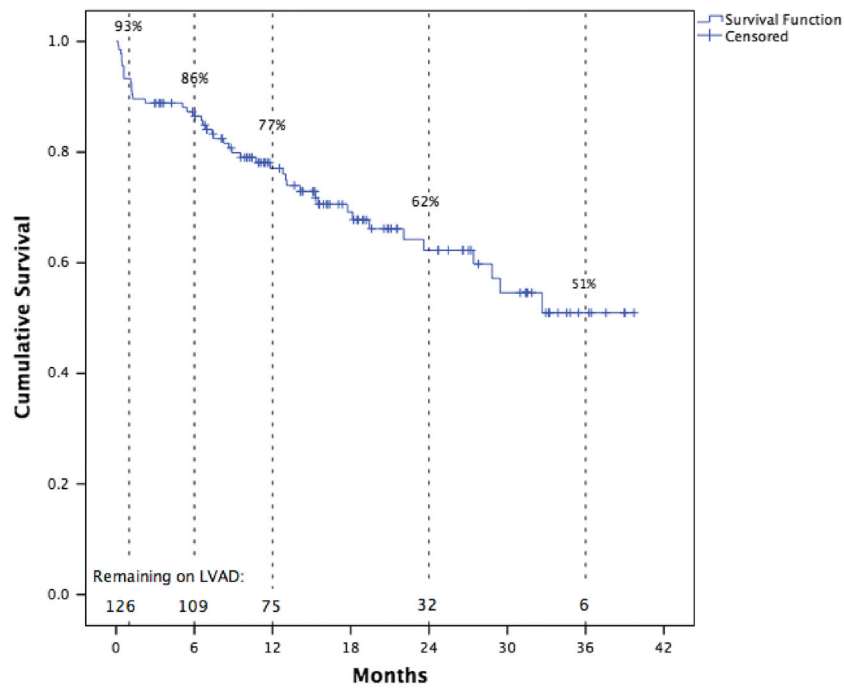
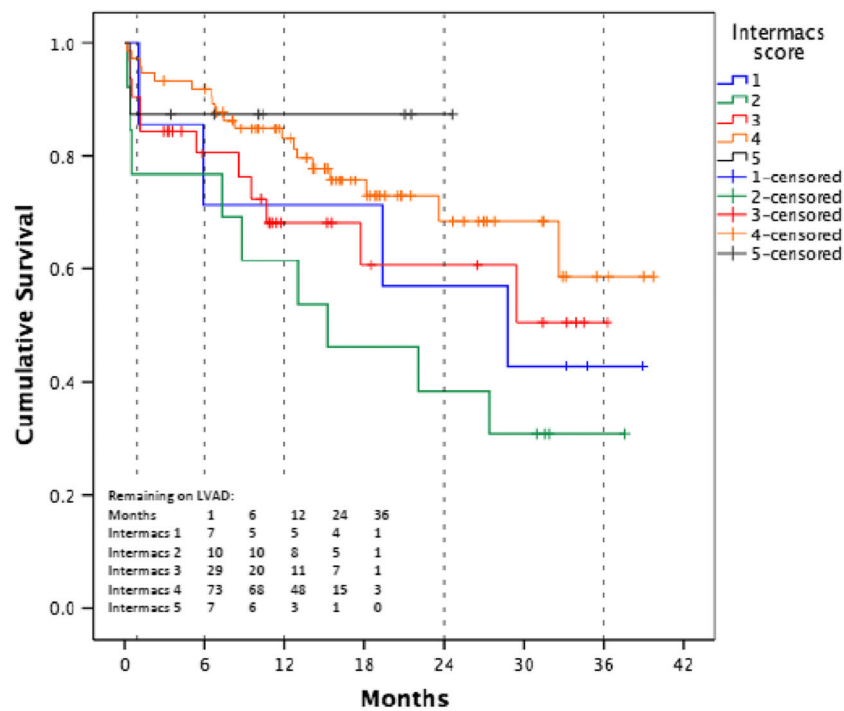
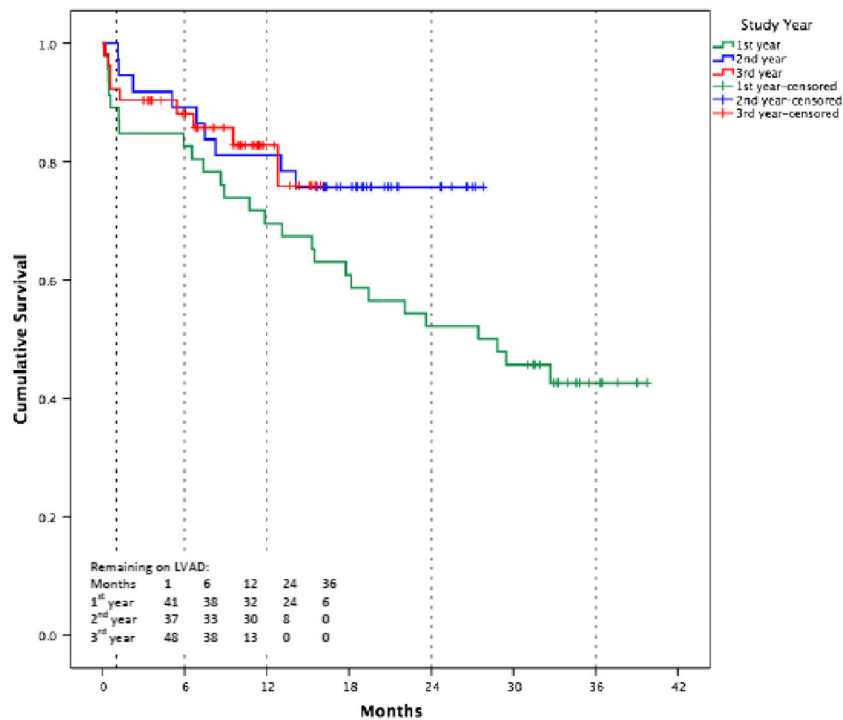


Figure 3 Kaplan–Meier analysis: Survival for LVAD patients by INTERMACS profile at baseline.



**Figure 4** Kaplan–Meier analysis: Survival for LVAD patients by year of program, in which the patient received implant.

stroke. Fourteen (10%) patients with stroke died. Surgery for intracranial hematoma was performed in two patients who were both discharged home. Fourteen patients (10%) had device thrombosis, and three of these patients required LVAD reimplantation during the first 30 days after initial implant.

As depicted in *Figure 1*, the majority of patients ( $n = 115$ , 76%) came from regions outside of Astana. One hundred twenty (89%) patients were discharged home, and the remainder died in hospital. There were 152 readmissions in 67 (50%) LVAD patients. The most common reason for readmission was driveline infection, and most of these occurred after month six. During the study period, 8 patients were successfully flown back to the NRCCS by chartered aircraft. These 8 patients were readmitted with stroke ( $n = 2$ ), LVAD thrombosis ( $n = 2$ ), multiorgan failure ( $n = 2$ ), gastrointestinal bleeding ( $n = 1$ ) and epistaxis ( $n = 1$ ).

## Discussion

The initiation of the VAD programme at NRCCS has provided an important therapeutic option to patients with heart failure in Kazakhstan. Strong governmental support has been a key factor in the initiation and development of our programme. By adopting new technologies and applying the results of our data we aim to reduce adverse events and improve outcomes in our patients.

Some clinical characteristics of our patients were similar to the patients in the INTERMACS database, with a few notable exceptions<sup>10</sup> The majority of our patients (54%) had INTERMACS profile 4 at baseline, whereas only 14% of patients in the INTERMACS database were INTERMACS profile 4. We implant earlier in patients because of the low likelihood of heart transplant, the large distances between our centre and many of our patients, and to prevent right ventricular failure. The percentage of patients with ICD/ cardiac resynchronization therapy in our population is lower than in some centres outside Kazakhstan, perhaps because of the fact that cardiac electrophysiology programmes in Kazakhstan began to develop recently. The mean age of our patients was similar to other recently published LVAD experience<sup>11,12</sup> The proportion of our patients with a DT indication was similar to the INTERMACS database. Fifty six percent of our patients received a VAD for the BTT indication; however, because of the lack of heart donors, transplantation is not common. Also, contributing to the low transplant rate is that patients are cautious about undergoing another surgical procedure after they have been stabilized on the VAD. For patients with the BTT indication, we sometimes perform coronary artery bypass graft during the VAD implantation procedure to revascularize the walls of the right ventricle because there is a low likelihood of a heart donor that is becoming available. We always perform valve repair if moderate to severe tricuspid valve or mitral valve insufficiency is present during implantation to prevent worsening of pulmonary hypertension and right ventricular failure.

Table 2 Adverse events listed by the percent of patients with events and the events per patient-year (EPY) of support; n = 135 (LVAD)

Cumulative support duration (patient-years)	Total			<30 days			>30 days		
	Patients with event, n (%)	No. of events	Events/ patient-year	Patients with event, n (%)	No. of events	Events/ patient-year	Patients with event, n (%)	No. of events	Events/ patient-year
Stroke, all	38 (28)	40	0.23	5 (3.7)	5	0.46	33 (24)	35	0.21
Ischemic stroke	23 (17)	25	0.14	5 (3.7)	5	0.46	18 (13)	20	0.12
Hemorrhagic stroke	15 (11)	15	0.08	0	0	—	15 (11)	15	0.09
Driveline infection, all	47 (35)	94	0.53	1 (0.7)	1	0.09	46 (34)	93	0.56
Medical treatment	34 (25)	76	0.43	1 (0.7)	1	0.09	33 (24)	75	0.45
Surgical treatment	13 (10)	18	0.10	0	0	—	13 (9.6)	18	0.11
Mediastinitis: VAD related	3 (2)	3	0.02	0	0	—	3 (2)	3	0.02
Pocket infections	2 (1.5)	2	0.01	0	0	—	2 (1.5)	2	0.01
Sepsis <sup>a</sup>	4 (3)	4	0.02	1 (0.7)	1	0.09	3 (2)	3	0.02
Reoperation for bleeding	10 (7)	11	0.06	10 (7)	11	1.02	0	0	—
Transfusion of RBC only <sup>b</sup>	23 (17)	27	0.15	23 (17)	27	2.5	0	0	—
GI bleeding	9 (7)	14	0.08	4 (3)	4	0.37	5 (3.7)	10	0.06
Epistaxis	11 (8)	11	0.06	5 (3.7)	5	0.46	6 (4.4)	6	0.04
Hemorrhoid	2 (1.5)	2	0.01	0	0	—	2 (1.5)	2	0.01
Device thrombosis, all	14 (10)	16	0.09	4 (3)	4	0.37	10 (7)	12	0.07
Medical treatment	8 (6)	10	0.06	1 (0.7)	1	0.09	7 (5)	9	0.05
LVAD reimplantation	3 (2)	3	0.02	3 (2)	3	0.28	0	0	—
HTx	1 (0.7)	1	0.01	0	0	—	1 (0.7)	1	0.01
Stop of the pump	2 (1.5)	2	0.01	0	0	—	2 (1.5)	2	0.01
RV failure	29 (21)	32	0.18	20 (14.8)	20	1.85	9 (6.7)	12	0.07
RVAD (LevitronixCentrimag) <sup>c</sup>	1 (0.7)	1	0.01	1 (0.7)	1	0.09	0	0	—
ECMO <sup>d</sup>	4 (3)	4	0.02	3 (2)	3	0.28	1 (0.7)	1	0.01
Arrhythmia	14 (10)	15	0.08	6 (4.4)	6	0.55	8 (6)	9	0.05
Atrial fibrillation/flutter	4 (3)	5	0.03	0	0	—	4 (3)	5	0.03
Ventricular fibrillation/tachycardia	10 (7)	10	0.06	6 (4.4)	6	0.55	4 (3)	4	0.02
Respiratory failure	9 (7)	9	0.05	8 (6)	8	0.74	1 (0.7)	1	0.01
Renal failure	27 (20)	27	0.15	19 (14)	19	1.76	8 (6)	8	0.05
Driveline damage required repair	3 (2)	3	0.02	1 (0.7)	1	0.09	2 (1.5)	2	0.01

Abbreviations: ECMO, extracorporeal membrane oxygenation; gastrointestinal; GI, heart transplantation; HTx, LVAD, left ventricular assist device; RBC, red blood cells; right ventricle; right ventricular assist device; RV, RVAD, VAD, ventricular assist device.

<sup>a</sup>This group of patients includes one case of VAD related mediastinitis.

<sup>b</sup>Transfusion of RBC during the first 7 days post implant:  $\geq 50$  kg:  $\geq 4$  U packed RBC within any 24 h period during first 7 days post implant;  $\leq 50$  kg:  $\geq 20$  cc/kg packed RBC within any 24 h period during first 7 days post implant.

<sup>c</sup>Not including patients with BiVAD.

<sup>d</sup>There was one case where RVAD LevitronixCentrimag with oxygenation was used.

All valve replacements are performed with biological prostheses. Radiofrequency ablation is performed according to recent guidelines.<sup>13</sup>

Approximately half of our patients receiving LVAD had right ventricular heart failure prior to LVAD implantation. If we cannot optimize right ventricular function preoperatively, the patient may still undergo LVAD implantation, and we generally set a lower threshold for RV implant. Our approach to long-term therapy of biventricular heart failure includes inotropic support and nitric oxide. If optimal pharmacologic therapy does not fully control the right ventricular heart failure, then we begin treatment with RVAD Levitronics Centrimag.

Survival rates were lower after 12 months on LVAD support in patients implanted during the first year of our programme. Patients implanted during the first year (2012) tended to have more severe INTERMACS profiles, and this may explain our observation. After the first year, we selected our patients differently such that patients with INTERMACS profiles 1 and 2 received short-term support devices and long-term support assist devices were given to patients with INTERMACS profiles 3 and 4. We believe that factors contributing to the better outcomes observed in years 2 and 3 are related to improvements in pre-operative treatment of patients, increase in experience and skill of team members.

The strength of our study is that we performed a high volume of VAD implants relative to other existing world cardiac surgery centres of excellence. However, our study is not without limitations, including that the analysis was retrospective. Our patient cohort was not large enough to develop models to identify predictors of adverse events; however, this is a relevant topic for future research. Other limitations are that the number of patients who continued on VAD support beyond 12 months was low, limiting the inferences that can be made from survival estimations beyond 12 months. Our study population has some differences with VAD populations reported in the clinical literature, therefore making it challenging to compare results of VAD populations from other centres. Notwithstanding, the differences in our study population compared

with other centres, observed survival and adverse event rates are not dissimilar to those reported by other centres.<sup>11–13</sup> Our VAD programme was developed before any heart transplantation programme existed in our country. The existence of the VAD programme is now stimulating the growth of heart transplantation in Kazakhstan. However, one of the main challenges we currently face is the low probability that our patients will receive heart transplantation. In addition, remote monitoring of LVAD patients is a unique challenge we face because of the large distances between our centre and our patients. We continue to develop methods to hone monitoring methods to improve patient outcomes.

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## Conflict of Interest

None declared.

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