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REVIEW

Left Ventricular Assist Device-Related Complications

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ABSTRACT

Left ventricular assist device (LVAD) has emerged as a safe, durable, and revolutionary therapy for end-stage heart failure patients. Despite the appearance of newer-generation devices that have improved patient outcomes, the burden of adverse events remains significant. Although the survival rate for patients with LVAD is appreciated to be 81% at 1 year and 70% at 2 years, the incidence of adverse events is also high. Over time, both early and late postimplant complications have diminished in terms of prevalence and impact; however, complications, such as infections, bleeding, right heart failure, pump thrombosis, aortic insufficiency, or stroke, continue to represent a challenge for the practitioner. Therefore, the aim of this review is to highlight the most recent data regarding the current use of LVAD in the treatment of end-stage heart failure, with a specific focus on LVAD-related complications, in order to improve device-related outcomes. It will also revise how to mitigate the risk and how to approach specific adverse events. Withal, understanding the predisposing risk factors associated with postimplant complications, early recognition and appropriate treatment help to significantly improve the prognosis for patients with end-stage heart failure.

Keywords: end-stage heart failure, mechanical circulatory support, ventricular assist device, complications, risk factors

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INTRODUCTION

Heart failure (HF) is a major public health issue, accounting for more than 1 million hospitalizations annually, both in the USA and Europe. Recent studies suggest that there is an increase in all-cause mortality and cardiovascular mortality with each rehospitalization for patients with heart failure.[1,2] Thus, it is very important to reduce the hospitalization rates in order to improve the patients' outcome.

Advanced HF is defined by the presence of a persistent symptomatology, refractory to maximum medical therapy, whose further management requires specialized strategies such as mechanical circulatory support, continuous inotropic infusion, or heart transplantation.[3] Despite major therapeutic advances, one-year mortality of these patients is still high, estimated at 33%.[4,5]

It's been 25 years since the Food and Drug Administration (FDA) has approved the introduction of left ventricular assist devices (LVADs) into clinical practice for the treatment of patients with advanced HF. A 10-times increase in LVAD implantation rate has been recorded between 2009 and 2019.[5,6] At the beginning, LVAD procedures were accompanied by an excess of morbidity and

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mortality. Over time, due to technological improvements, both early and late postimplantation complications have diminished in terms of prevalence and impact.[7] The burden of adverse events (AEs) remains however a critical hurdle to the widespread use of LVADs. The 1-year survival rate is similar for LVAD procedures vs. heart transplantation in patients with end-stage HF; however, the long-term outcome associated with these procedures is still a matter of debate.[8–11]

Therefore, the aim of this review is to highlight the most recent data regarding the current use of LVADs in the treatment of end-stage HF, with a specific focus on LVAD-related complications. It will also revise how to mitigate the risk and how to approach specific AEs associated with this procedure.

LVAD-RELATED COMPLICATIONS

LVAD-related complications are important causes of morbidity and mortality in patients with end-stage HF. They can be systematized into three major categories:

- complications related to the pump and its components (e.g., pump malfunction);
- complications related to the patient (ventricular arrhythmias, valvular insufficiency, and right ventricular failure);
- pump-patient interface-related complications (acquired von Willebrand disease, infection, stroke, and pump thrombosis).[12–14]

In the first 60 days after implantation, the most frequent complications are bleedings, infections, and arrhythmias, followed by respiratory and neurologic events, reoperations, and tamponade. Bleedings and arrhythmias tend to precipitate immediately after the intervention, while infections and neurologic events appear to have a gradual beginning.[15]

According to the 8th annual INTERMACS report, the rate of rehospitalization has been estimated to be 60% at 6 months postimplantation and 65% to 80% at 1 year after the procedure.[16] This manuscript will further focus on reviewing the most important device-specific complications.

1. INFECTIONS

Infections are common LVAD-related adverse events, representing independent predictors of mortality.[17] They may occur at any level of the LVAD, extending from local to systemic infection and sepsis.[18,19] Although significant progress was made in the area of ventricular assist device technology, infections are still an important source of morbidity, requiring not only antibiotherapy, but frequently driveline debridement, incision and drainage of the pocket, or even device explantation.[17]

Bloodstream infection, a serious complication of LVAD implantation, is a risk factor for stroke and is associated with a high mortality.[20] LVAD-associated endocarditis demands device removal if sepsis, septic emboli, or end-organ dysfunction occur.[17]

It is deemed that driveline infection, in the soft tissue surrounding the outlet, is the most prevalent, ranging from 15.4% to 23.8%.[20,21] However, these numbers are indicating an extraordinary improvement when compared to the results of the REMATCH trial, where driveline infection occurred in 41% of cases.[22]

A comprehensive analysis of the MOMENTUM 3 study pointed that female gender, usage of pre-implant intra-aortic balloon pump, personal history of cardiac surgery, and obesity are independent risk factors for major infectious complications in the first 2 years post-intervention.[23]

A study including 437 patients with advanced HF who underwent implantation between May 2009 and March 2016 with either HeartMate II (n = 314) or HeartWare HVAD (n = 123) attempted to quantify the incidence of severe infections and their implications on survival. The percentage of severe pump infections was remarkably higher in the HeartMate II group (50% vs. 23%), but it did not impressively affect survival. *Staphylococcus* species, *Pseudomonas* and *Enterococcus* were the most common pathogens involved in the development of pump infections. Regarding the driveline infections, the most frequent cultured bacteria were *Pseudomonas*, *Staphylococcus* species and *Serratia*.[18]

The diagnosis of LVAD-related infection is challenging, the conventional evaluation of this major AE consisting mainly of a complete blood count, a chest radiography, and three sets of blood cultures collected over a period of 24 hours. Gram stain and culture of the site should be performed whenever there is a suspicion of pump or driveline infection, C-reactive protein and erythrocyte sedimentation rate having additional value.

A single-center, retrospective case series study led by Tam *et al.* aimed to identify the accuracy of fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in diagnosing device-related infections. FDG PET/CT scans performed on LVAD receivers between September 2015 and February 2018 at the University of Michigan were evaluated. The authors con-

cluded that FDG PET/CT scans should be integrated into the current diagnostic algorithm as an imagistic method of high sensitivity. However, the specificity of the test needs to be improved in order to obtain superior results.[24]

2. BLEEDING

With regard to hemocompatibility-related AEs, the HeartMate 3 device nearly abolished the risk of pump thrombosis and was associated with a lower incidence of strokes. Even though there was a considerable reduction in bleeding complications, the residual risk of hemorrhagic events continues to be of the greatest importance.[13] Up to now, bleeding is the most common AE, appearing in 30–60% of cases, both early and late after LVAD procedure.[25]

After implantation, distinguishing between diffuse coagulopathy and surgical bleeding is mandatory given that these two conditions require different therapeutic approaches. In case of bleeding produced by coagulation disorders, the use of recombinant factor VII must be weighed against the crucial risk of thromboembolic events, especially at higher doses. When cumulative chest tube outputs are greater than 200 mL per hour in patients with normal or corrected coagulation parameters, surgical bleeding can be claimed. As massive blood transfusion can lead to the development of right heart failure, early re-exploration and delayed sternal closure have been suggested.[17]

Gastrointestinal bleeding (GIB) is however the most frequent type of bleeding, affecting especially the elderly with previous history.[25] Irrespective of anticoagulation requirement following LVAD implantation, multiple mechanisms seem to be involved in the etiopathogenesis of GIB, including acquired von Willebrand syndrome and arteriovenous malformations.[26] The high shear stress produced by the rotational speed of the LVAD is responsible for the loss of high-molecular-weight multimers of von Willebrand factor (HMvWF), converting it into an easy target for cleavage by proteolytic enzymes, especially by ADAMTS-13. Deprivation of HMvWF weakens platelet binding and puts patients at high risk of bleeding. Also, it is considered that the non-pulsatile blood flow generated by the late-generation LVADs causes a decrease in intraluminal pressure and a dilatation of the mucosal veins, giving rise to arteriovenous malformations as previously reported for aortic stenosis.[27]

Current guidelines advocate for performing a colonoscopy or upper endoscopy as part of the diagnostic assessment of GIB. Regarding the therapeutic management of LVAD-related GIB, both nonpharmacologic and pharmacologic interventions are valuable. Presumably, the most important nonpharmacological approach consists in lessening pump speed as an attempt to obtain pulsatility while preserving satisfactory left ventricular unloading. Apart from volume expansion, discontinuation of antiplatelet and anticoagulation therapies is controversial because of the coexisting risks of pump thrombosis and thromboembolic events.[26]

For recurrent GIB, refractory to conventional treatment, other therapeutic strategies have been proposed including octreotide, thalidomide, hemodynamic optimization by the ramp test, and fish oil therapy. Optimizing LVAD speed through a ramp test may help suppressing GIB, as hemocompatibility-related AEs are generally influenced by hemodynamics. The fish-rich diet, containing fish oil and omega-3, seems to be the main explanation for lower LVAD-related GIB in Japanese patients.[28]

A prospective study, including 30 LVAD patients, evaluated octreotide's capability of reducing the frequency of recurrent GIB. All study participants received an intramuscular injection of 20 mg octreotide every four weeks, as secondary prevention, for recurrent gastrointestinal bleeding despite repeated transfusions and conventional medical treatments. There was a reduction in the number of GIB, despite maintaining the same antiplatelet treatment in parallel with increasing the levels of anticoagulation therapy.[29]

In a retrospective study of 24 continuous-flow LVAD recipients, the average number of arteriovenous malformations-associated gastrointestinal re-bleeding events was reduced in those on thalidomide therapy, which also resulted in fewer packed red blood cell transfusion requirements. However, inherent side effects of thalidomide should always be considered before the introduction of this treatment.[30]

Of note, patients with LVAD also carry a significant risk of intracranial hemorrhage, which is associated with a high mortality and poor prognosis.[31] Conventionally, it is considered that the level of anticoagulation used in the LVAD population with the purpose of preventing pump thrombosis is an independent risk factor for major bleeding. These major bleedings are defined by the presence of intracranial hemorrhage or any bleeding event requiring 2 units of packed red blood cells within 24 h, or bleeding that results into death. Contrastingly, a retrospective analysis of 85 patients implanted with Heartmate II between January 2009 and June 2014 at the Medical University of South Carolina, suggested that the incidence of nonsurgical major bleeding (occurring >7 days after implant) was not considerably interconnected with the degree of anticoagulation. The greatest risk of bleeding

pertained to those with low body weight, impaired kidney function, reduced hemoglobin at baseline, and also to those with dual antiplatelet therapy.[32]

Therefore, regarding the LVAD-associated bleedings, a multimodal approach of all etiological determinants and comorbidities is necessary in order to minimize their impact.

3. PUMP THROMBOSIS

Pump thrombosis (PT) is another well-known complication following LVAD implantation. It can result in rapid clinical deterioration or even demand of emergent pump exchange. Several studies focused on elucidating the predisposing factors and on developing useful diagnostic tools for PT.[33–38]

Three different types of LVAD-related blood flow obstructions were described: pre-pump, intra-pump, and post-pump thrombosis, with occlusive thrombus located within the inflow cannula, the pump itself, and at the level of the outflow graft.[33]

PREVENT (PREVENtion of HeartMate II Pump Thrombosis Through Clinical Management) was a prospective, multi-center, single-arm, non-randomized study of 300 patients implanted with HeartMate II. It demonstrated that a lower incidence of confirmed PT at 3 months could be obtained through the implementation of a pre-established set of medical and surgical recommendations, such as implant techniques, anticoagulation strategies, and pump speed management.[35]

The echocardiographic ramp test is popularly used for the detection of suspected LVAD thrombosis. An auxiliary echocardiographic ramp test, assessing the systolic to diastolic (S/D) ratio of the outflow graft flow, has been proposed as a novel method of recognizing PT.[36] Lactate dehydrogenase promises to be a helpful biomarker not only for diagnosing, but also for predicting PT, in both early and late hazard phases.[37] Neutrophil to lymphocyte ratio (NLR) increases significantly if a patient develops infection, stroke, or pump thrombosis, when compared to the NLR after 4–6 months of LVAD support. The greater the NLR value is at 4–6 months after LVAD implantation, the higher the risk of mortality.[38]

As atrial fibrillation (AF) and heart failure often coexist and foster each other, there were various attempts of evaluating the effect of preoperative AF on clinical outcomes after LVAD implantation. Surprisingly, a recent meta-analysis reported an increased risk of GIB in LVAD patients with concomitant AF, but not of PT or thromboembolic events.[39] A Japanese study sought to assess the relationship between AF and hemocompatibility-related AEs in HeartMate II recipients and proved that survival free from hemocompatibility-related AEs was similar, regardless of the presence of pre-implantation AF.[40]

Another arrhythmia that closely accompanies the LVAD population is ventricular tachycardia (VT). It is estimated that approximately one third of patients develop ventricular arrhythmias after continuous-flow LVAD implantation.[41] Thereby, a recent survey aimed to measure PT, stroke, and embolic event rates after VT ablation. Patients assigned to endocardial ablation between 2009 and 2016 experienced increased rates of device thrombosis and embolic events compared to the control group with VT who were not ablated.[42]

An algorithm especially designed for an optimal diagnosis and treatment of PT advises on using washout maneuver for pre-pump obstruction, thrombolysis and pump exchange for intra-pump thrombosis, and stenting for post-pump occlusion.[33]

Antiplatelet and anticoagulation therapies are assigned to LVAD recipients in order to prevent hemocompatibility-related AEs. Because the optimal dose of aspirin (ASA) following HeartMate 3 implantation is still disputable, a secondary analysis of MOMENTUM 3 compared the efficacy of the usual dose (325 mg) with that of the low-dose (81 mg) ASA in terms of survival free from non-surgical bleeding, PT, stroke, and peripheral arterial thromboembolic events at two years. Both usual- and low-dose ASA showed comparable rates of bleeding and thrombotic events.[43]

In a prospective late study, LVAD patients underwent invasive hemodynamic measurements in order to evaluate the impact of decoupling between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure on hemocompatibility-related side effects and also on right heart function. Decoupling was indicated by the presence of a difference of >5 mmHg between diastolic pulmonary artery pressure and pulmonary capillary wedge pressure. The decoupling group had higher incidences of hemocompatibility-related AEs. That being the case, a therapeutic approach of decoupling is desired.[44]

4. STROKE

Stroke remains an indelible cause of death following mechanical circulatory support (MCS) implantation. Corresponding to a survey of the INTERMACS database (Interagency Registry for Mechanically Assisted Circulatory Support), from June 2014 to June 2017 there were 9,489 patients receiving continuous-flow LVADs. Through June

2018, the follow-up period, 1,515 (16%) of the recipients were afflicted with 1 or more strokes. The risk of stroke was approximated at 4% for the first month, 9% during the first 6 months, and at 14% in the first year. An obvious increase in the 1- and 2- year mortality was observed in patients with an initial disabling stroke vs. non-disabling stroke, as judged by the Modified Rankin Score.[45]

Even though the final report of MOMENTUM 3 demonstrated the superiority of HeartMate 3 with regard to the incidence of either ischemic or hemorrhagic stroke, when compared to HeartMate II, this condition persists on being a major shortcoming of LVAD therapy, linked to high morbidity and mortality.[21,46]

ENDURANCE was a randomized controlled trial that proved the non-inferiority of HeartWare against HeartMate II with regard to survival free from disabling stroke or device removal for malfunction or failure. A secondary analysis of the ENDURANCE DT trials examined the subtypes of stroke that occurred in the HeartWare LVAD cohorts and identified major modifiable risk factors. Over 2 years, 29.5% of recipients had at least one neurologic event. Hemorrhagic cerebrovascular accidents (HCVAs) affected 7% of the study population and were affiliated to no aspirin usage, both supra- and sub-therapeutic international normalized ratio (INR) values, and prior stroke or transient ischemic attack (TIA). Fifteen percent of the recipients suffered from an acute ischemic stroke (AIS), with peripheral vascular disease, INR <2, and the presence of left ventricular thrombus being independent, determinant factors. The omission of aspirin from the antithrombotic regimen was associated with both HCVA and TIA. The trial underlined the importance of maintaining, by all means, the hemostatic homeostasis.[47]

The connection between infection and stroke in patients with LVADs has been exhaustively decomposed by numerous studies. However, it is probably worth mentioning that in a prospective cohort study design, driveline or pump pocket infection did not seem to be bounded with the emergence of stroke. AISs were particularly interrelated with wound infection and bloodstream infection, while HCVAs were associated with bloodstream infection in 100% of cases.[48]

Transcranial Doppler ultrasound emboli monitoring (TCD-e) is a noninvasive technique valuable in recognizing the presence of microembolic signals (MES). A prospectively collected database consisting of 515 LVAD patients assessed the relationship between cerebral microembolization identified by the TCD-e examination and acute ischemic events. In this study, 184 participants developed either AIS or TIA, with 35 (7%) of them benefitting of TCD-e exploration, generally at a median of 1 day after the occurrence. MES were described in 15 (44%) of the TCD-e evaluations, with a median MES count of 4. Accordingly, the prevalence of MES was high among the LVAD recipients that developed neurological events. Hence, the authors drew attention to the fact that a great frequency of MES might indicate a prothrombotic status and that more research is needed.[49]

Statins have a central position in the therapeutic arsenal against both cardiovascular and neurological events such as stroke. Thereby, a single-center, retrospective, observational, cohort study including 200 subjects implanted with a durable continuous-flow LVAD between May 2008 and March 2018 appraised the impact of statins on the rate of stroke in this particular population. An inverse association between statin usage and ischemic neurological events has been described. In light of the above, it was stated that the prescription of statins should not be discontinued if there is a pre-existing indication.[50]

5. AORTIC INSUFFICIENCY

Aortic insufficiency (AI) is a high-priority complication following LVAD implantation that persisted on being both prevalent and of great significance during HeartMate 3 support.[51] The risk of developing significant AI is increased among those with preexisting aortic regurgitation and once extended augments the rate of mortality together with the incidence of hemocompatibility-related adverse events.[52,53]

Accepted surgical techniques to rectify AI in patients implanted with continuous flow LVADs are represented by central aortic oversewing, complete aortic valve closure, patch closure of the ventriculo-aortic junction and aortic valve replacement with a bioprosthesis.[54]

Transcatheter aortic valve replacement (TAVR) came across as an appealing option for those with serious risk for surgical valve replacement, with satisfactory immediate and medium-term outcomes.[55] A single-center experience, utilizing TAVR to treat symptomatic AI in LVAD-recipients, reported valve migration warranting a second valve for stabilization, retroperitoneal and groin hematoma, and pseudoaneurysm demanding thrombin injection as being the most common procedural complications.[56]

ADVERSE EVENT CLUSTERING

Over time, the field of LVAD devices has undergone various paradigm changes consistent with a decrease in the number of persons experiencing AEs. The high burden of com-

plications remains however an issue of concern, demanding further research, only 30% of the recipients being free of any side effect within one year after implantation.[57]

The majority of LVAD studies directed their attention only to individual AEs, neglecting a possible interrelation or causality which may exist between them. In 2019, Movahedi *et al*. reported for the very first time the existence of sequential chains of AEs following LVAD delivery. By analyzing 58,575 recorded AEs of 13,192 patients receiving a continuous-flow LVAD between 2006 and 2015 in INTERMACS, seven groups of sequential chains of AEs were identified, each distinguished by the presence of a dominant AEs or multiple AEs, showing up in a certain order, as presented in Table 1.[58]

One year later, a large, multicenter study evaluated if there is any temporal relationship between AEs after LVAD implantation and documented that most in-hospital AEs are linked to the development of subsequent AEs. The study included 18,763 patients, implanted between 2006 and 2016, registered in the INTERMACS, and only the AEs occurring during the index-hospitalization for the LVAD surgery were analyzed. Primary renal or respiratory failure had the strongest positive association with the development of consequent AEs, with the lowest 1-year survival after LVAD insertion. Therefore, the study pointed out the desirability of targeting these two conditions, in order to restrain the overall AE boost. Bleeding, infections, and right ventricular assist device insertion were also accompanied by sequential complications, but the magnitude was less significant.[59]

TEMPORARY MECHANICAL CIRCULATORY SUPPORT AND IMPELLA

Cardiogenic shock (CS) is not a singular disease, but a multisystemic disorder portrayed by critical peripheral hypoperfusion due to primary cardiac dysfunction. Except for drug therapy, more aggressive strategies, such as temporary MCS, have become available lately. Popularly used percutaneous assist devices include intra-aortic balloon pump, a pulsatile percutaneous ventricular assist device (iVAC), veno-arterial extra-corporeal membrane oxygenation, Impella, and TandemHeart.

Impella is a continuous-flow, axial pump that supplies blood from the left ventricle to the ascending aorta. It is ordinarily percutaneous, delivered via the femoral or axillary artery with the purpose of increasing cardiac output and coronary blood flow.[60]

Nowadays, various models of Impella devices have been conceived based on the insertion site and the maximal flow rate. Impella 2.5 and Impella CP have a lifespan of maximum 4 days, while Impella 5 can be used for up to 6 days. However, Impella 5 is surgically implanted and runs at the highest flow rate of 5 L/min. Another heart pump type, conventionally utilized in case of right ventricular failure, is Impella RP. Transesophageal echocardiography guidance is of utmost importance throughout the positioning procedure.[61]

Usually, Impella operates as a bridge to either recovery, transplant, or durable LVAD implantation. A study involving 57 patients reviewed the clinical utility, indications,

TABLE 1. Sequential chains of AEs in the INTERMACS analysis of 58,575 recorded AEs of 13,192 patients – the groups resulted from hierarchical clustering and their main characteristics

Group number	Name	Main characteristics
Group 1	Recurrent bleeding	862 subjects with a minimum of 2 bleeding AEs
Group 2	Trajectory of device malfunction & explant	1,591 recipients who had device malfunction, preceded by two types of AEs including infection and bleeding and finally had their LVADs explanted
Group 3	Infection	3,438 patients who suffered mostly from infections
Group 4	Trajectories to transplant	3,302 individuals who received a heart transplant; their AEs mostly consisted in bleeding, infection, and cardiac arrhythmia
Group 5	Cardiac arrhythmia	1,275 persons who had one or more arrhythmic events along with infection and bleeding
Group 6	Trajectory of neurological dysfunction & death	1,616 recipients with high mortality caused especially by hemorrhagic strokes
Group 7	Trajectory of respiratory failure, renal dysfunction & death	1,108 subjects who died with an average of 3 and 5 AEs; The presence of both renal and respiratory failure.

AE – adverse events; LVAD – left ventricular assist device

and outcomes of Impella devices. It appeared that cardiogenic shock associated to acute coronary syndrome, end-stage cardiomyopathy (dilated or ischemic), and myocarditis were the dominant causes. Hemodynamic response was achieved within 24 h of MCS with Impella, along with the recovery of both renal and liver function.[62] New emerging evidence indicates that Impella CP might be of real benefit when used as a bridge to recovery for non-ischemic CS, with overall mortality comparable to that reported in current large shock trials.[63]

Additionally, Impella serves as hemodynamic support during high-risk percutaneous coronary interventions (PCIs). Sixty-one subjects were enrolled in a study that intended to evaluate the incidence and predictors of vascular access site complications for patients undergoing high-risk PCI with Impella protection. Only 5.8% of the participants experienced major bleeding and only one person necessitated erythrocyte concentrate transfusion, while superficial hematoma was documented in 95% of the cases. Apparently, operating under a standardized protocol leads to a low frequency of vascular complications.[64]

Impella seems to be a reasonable therapeutic approach also for peripartum cardiomyopathy (PPCM). Fifteen women with PPCM, presenting severe heart failure and a mean ejection fraction of 14.7 ± 6%, were included in a retrospective analysis that focused on evaluating the application of Impella as a bridge to recovery or implantation of durable LVADs. Two women died (13.3%), while 13 (87.7%) remained alive. Eight of them (53.3%) had a recuperation of heart function, while 6 (40%) were bridged to durable MCS implantation, these results inciting the further usage of Impella in the PPCM population.[65]

On the contrary, a recent meta-analysis compared Impella to intra-aortic balloon pump counterpulsation or medical treatment in CS after myocardial infarction or cardiac arrest and demonstrated that the use of Impella is accompanied by higher rates of bleeding and peripheral ischemic complications when used in inappropriate circumstances, for low risk CS.[66] The baseline serum lactate level, as well as the necessity of vasopressors and inotropes, are individual predictors of increased mortality in subjects implanted with Impella for acute severe CS. Serum CO_2 and pH are of additional value in appraising mortality.[67]

CONCLUSIONS

LVADs represent an ultimate, revolutionary therapy for advanced HF. Extensive technical enhancements have been brought over the years, standing for better survival rates and also a decline in the burden of complications. Even with the late-generation devices, device-related AEs continue to represent an important cause of morbidity and mortality. Nevertheless, understanding the predisposing risk factors combined with a precocious recognition and a standardized approach, helps to improve the overall prognosis.

CONFLICT OF INTEREST

We declare that there is no conflict of interest.

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