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HEMORRHAGIC AND THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH IMPLANTED LEFT VENTRICULAR ASSIST DEVICES IN EARLY POSTOPERATIVE PERIOD

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Abstract. The work is devoted to study hemorrhagic and thromboembolic complications in early postoperative period after implantation of left ventricular assist devices (LVAD).

We performed retrospective analysis of 10 patients, males aged 55±13.5 years, with a BMI of 30.8±8.3, with a left ventricular ejection fraction ranging from 9% to 28%, which in the period from 11.03.2016 to 22.11.2017 year, in the Silesian center of the Heart Disease (Poland), in conditions of artificial blood circulation, LVAD was implanted.

In the early postoperative period, patients received daily anticoagulant target therapy (ACCT), consisting of the following drugs: heparin (6-11 U/kg/h), aspirin (75-150 mg), Clopidogrel (75-150 mg), warfarin (1.5-7 mg), Nadroparinum Ca (0.3-0.6 ml/twice on day), Fondaparinux Na (2.5-5 mg/twice on day). Two patients received mono-heparin therapy, one patient received monotherapy with warfarin for 14 days. Other patients during the same period received combined heparin therapy in the first three days with a subsequent transition to warfarin, aspirin, Clopidogrel, Fraxiparin, or thrombin blocker.

The mechanical support of the left ventricle was carried out essentially by two different implantable systems, performing one function of support of the left ventricle: POLVAD – programmed controlled pneumatic membrane mechanical circulation of blood to two patients, and LVAD program-controlled electro-centrifugal circulation for eight patients. The duration of support by POLVAD system was from 102 to 156 days. Length of support – LVAD ranged from 20 to 78 days.

A comparison of the analyzed results led to the conclusion that anticoagulant mono-therapy with heparin or warfarin leads to an increase in the percentage of complications and mortality compared with the alternative combination anticoagulant targeted therapy consisting of the following drugs: heparin (6-11 U/kg/h), aspirin 75-150 mg), Clopidogrel (75-150 mg), warfarin (1.5-7 mg), Nadroparinum Ca (0.3-0.6 ml/ twice on day), Fondaparinux Na (2.5-5 mg/ twice on day), Where survival rates were significantly higher by 60%.

Key words: left ventricular assist device (LVAD), anticoagulant targeted therapy (ACTT), hemorrhagic and thromboembolic complications.

INTRODUCTION

Despite the possibilities of modern medicine in the field of transplantology of the heart, the number of necessary donor grafts is quite limited. As a result, the number of patients in the waiting lists significantly increasing, this is often accompanied by preoperative mortality [1]. The use of the systems of long-term mechanical support for blood circulation as a bridge to heart transplantation gives a chance to save lives of the patients with severe degrees of heart failure refractory to medical therapy. Mechanical blood circulation support not only stabilizes the hemodynamic function, but also normalizes the function of other organs (liver, kidney) [2]. However, the implantation of left ventricular assist devices (LVAD) is associated with various short- and medium-term complications, before and after thirty days.

Currently, the Silesian Center of Heart Disease (Poland) uses the most modern autonomous devices for circulatory mechanical blood circulation support at the level of the world practice. POLVAD – a

programmed controlled pneumatic membrane mechanical blood circulation system developed by a group of engineers led by great Z. Religa – allows maintaining a reduced function of both right and left ventricles of the patient's heart. With the aid of a cannula it connects to the heart and trunk vessels being outside the patient's body, resulting in monitoring the operation of the device (Fig. 1).

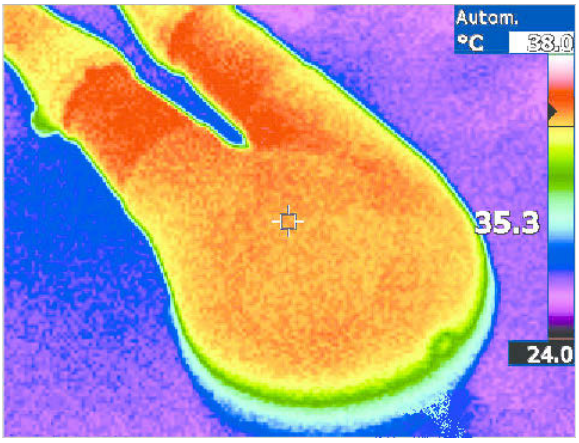

Fig. 1. Thermogram of programmed-controlled pneumatic membrane mechanical system of blood circulation POLVAD, which allows to detect thrombosis of the device.

The study involved two patients with left ventricular support with POLVAD-MEV. Another type of auxiliary support for the left ventricle is the LVAD-centrifugal-angle type, such as HeartMate® III, Thoratec ©, and HeartWare® III (USA). They have a compact look are compared to previous models, so they are used more often in the world practice. Studies initiated by the manufacturers of these devices indicate 83% of patient survival after implantation of devices of this type, 10% of possible events of cerebral circulation and only one percent of events of thrombosis of pump engine device [24]. At the same time 78% of patients have improved cardiac function by switching from NYHA IIIB / IV to NYHA I / II [24].

Major non-surgical adverse events and complications during LVAD implantation include bleeding, thrombosis of the pump of LVAD device, ischemic and hemorrhagic stroke, renal dysfunction, multiple organ failure and infection, which are the main causes of fatal cases [3]. Regarding the timing of complications after LVAD implantation – they can be early (up to 30 days after implantation) or late (30 days after implantation).

Target. The aim of our study was to investigate the correlation between hemorrhagic and thromboembolic complications and the state of the blood coagulation system in patients undergoing LVAD implantation in the context of other algorithm of the anticoagulant therapy.

Materials and methods. The subject of the study was 10 patients, males, 55 ± 13.5 years old, with a body mass index of 30.8 ± 8.3 m 2, with a left ventricular ejection fraction ranging from 9% to 28%, who had implant LVAD in the period from 11.03.2016 to 22.11 .2017 in the Silesian Center of the Heart Disease (Poland), in conditions of artificial blood circulation. In five of the patients who was examined, had been implanted of devices for resynchronizing therapy with defibrillator-function ICD (

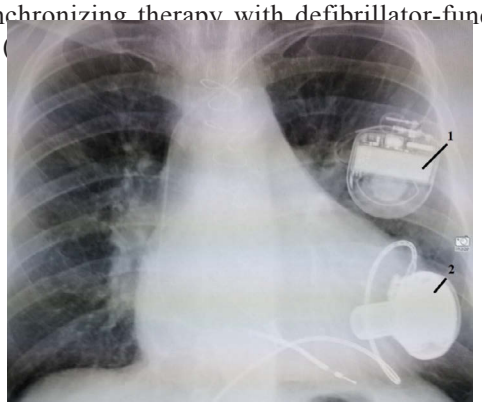

Fig. 2. Chest X-ray of patient P. with implanted LVAD device with centrifugal type and cardioverter-defibrillator.
(Note: 1 – ICD, 2 – left ventricular support device (LVAD)).

The physical state of patients corresponded to 6-14 points of the EUROSCORE. Depending on the status of INTERMACS, Level 1 (cardiogenic shock) was observed in 6 patients, Level 2 (progressive circulatory failure) – in 4 subjects. High pre-transplant pulmonary hypertension (transpulmonary gradient greater than 15 mm Hg and / or pulmonary vascular resistance greater than 4 Un of Wood) was detected in 7 patients. Two patients were operated in a condition of circulation delay with event of cardiopulmonary resuscitation, and one – on event of ventricular fibrillation.

The patient was operated with artificial blood circulation, and moderate hypothermia with t H" + 31 °C. The device productivity of artificial blood circulation was H" 2.5 l / min / mI. In order to protect the myocardium, Schtokert (Germany) alternating current systems were used to create artificial fibrillation at a frequency of 50Hz, 12V / 25A.

Monitoring of systemic hemodynamic was performed using IntellsVue X2 Philips™ (Netherlands) systems, Cardiac output & indexes – using the "A7Vigileo Monitor-Accesories EDWARDS LIFESCIENCES ™ systems" system, cerebral oxygenation – INVOS Oximetr Somanetics™ Inc. (USA).

The operation was conducted in conditions of epy- combined endotracheal anesthesia in a semi-

closed circuit with the purpose of maintaining the concentration of inhaleted anesthetics according to the age-old MAC-index. For intravenous anesthesia, fentanyl was used in a dose of 1.7 ± 0.8 мg/kg/min. or sulfentanil 0.015 ± 0.03 мg/kg/min.

For the patients with high pulmonary hypertension, had been inhaleted supply of NO under the control of EZ-Kinox Air-Liquide device (USA)., in a dose of 10-200 ppm, was used for up to several days in the postoperative period.

At the end of the operation, the artificial ventilation in the separation of intensive care (IT) was performed on the Dragger Evita V300 apparatus by air-oxygen mixture with oxygen concentration depending on the degree of pulmonary hypertension, under the control of the blood gas analysis, which was determined on the device ABL800 (France).

The analysis of the dynamics of the myocardium was determined by the analysis of blood lactate, troponin, and MB fraction of creatinine phosphokinase. All of the above analyzes and analysis of the blood coagulation system was performed at the Multiplate® Roche System Laboratory (France).

The average duration of blood circulation support with LVAD was 49.7 ± 28.2 days.

In the early postoperative period, LVAD patients received anticoagulant targeted therapy (ACTT) every day that consisted of the following drugs: heparin (6-11 Un/kg/h), aspirin (75-150 mg), Clopidogrel (75-150 mg), Warfarin (1.5-7 mg), NadroparinumCa (0.3-0.6 ml/2 ppm), Fondaparinux sodium (2.5-5 mg/2pc/d). Two patients received mono-heparin therapy, one patient received monotherapy with warfarin during the 14 days studied. The other patients received combined heparin therapy in the first three days with a subsequent transition to warfarin, aspirin, Clopidogrel, Fraxiparin, or thrombin blocker. Control of drainage fluid from pericardial and thoracic cavity was carried out on the system of two-chamber active drainage systems connected to constant negative pressure, which facilitated the withdrawal of the fluid and improved hourly calculation of its amount.

The results of the early postoperative period in patients with different types of ACTT experienced have a rather diverse picture of the response to anticoagulant targeted therapy.

On comparison, the patients were divided into groups that used standard anticoagulant targeted therapy with heparin or warfarin or in combination with acetylsalicylic acid (ASA) and alternative therapies for combination therapy with heparin in the first three days with a subsequent transition to warfarin, ASA, Clopidogrel, Fraxiparin, or thrombin blocker.

As can be seen from Table №1, 80%, 8 patients had the first week of heparin therapy on a steady inject-pump on rate from 6 to 11 Un/kg /h., and 20%, 2 patients were on heparin monotherapy at the all-time in ICU. Half of the patients in the first week and 70% (7 patients) of patients in second week had antiviral anticoagulant support with Warfarin at a dose of 1.5-7 mg / day.

As an alternative to the standard scheme of ACTT, the following drugs were used: 50% (five patients) received throughout the period aspirin at doses of 1.4 ± 0.7 mg / day; 30% (three patients) in the first week and 50% (five patients)of patients at the second week received Clopidogrel 1.3 ± 0.8 mg / day; Nadroparinum Ca (0.3-0.6 ml/2 g/d.) and Fondaparinux Na (2.5-5 mg/2 g/d) (Table 1).

In the first days of heparin therapy in 10% of one patient, there was a pronounced heparin-induced thrombocytopenia (HIT), which led to a change in the strategy for alternative therapy with Nadroparinum Ca. Subsequently, in this patient, gastro-intestinal bleeding (GIB) with uncertain localization was detected.

20% (two patients) with mono-heparin therapy had a reoperation after a huge drainage of amount of exudate after 2-3 days. In both, the postoperative period was complicated by neurology deficit. One of the two patients has severe cerebrovascular complications in the form of a large hemorrhagic stroke in the brain, and hepatic insufficiency. Both

Table 1. *Comparison of patient groups by quantity and quality of ACCT.*

Drugs	Control group of patients with classic ACTT (N= 5)			Study group of patients with classic ACTT (N= 5)		
	n=2	n=1	n=2	n=2	n=2	n=1
Heparin	+		+	+	+	+
Warfarin		+	+	+	+	+
ASA			+	+	+	
P1Y12-bl.				+	+	+
anty-Xa					+	+

Note: *ACCT - classical anticoagulant targeted therapy; anty-Xa - Nadroparin Sa; ASA - aspirin; P1Y12-b. - clopidogrel.*

patients died at 92 ± 57 days after and LVAD implantation.

The patients with combined standard classical therapy, 2 patients, which contained three days of heparin 6-11 IU / kg / day. with the transfer to the indirect anticoagulant warfarin and aspirin, in half of the cases had nephrotic events. One patient in this group received ischemic cerebrovascular disorder, which complicated the course of the post-operative rehabilitation. One patient (14.3% of cases) received some event of pump-thrombosis of device engine, with the subsequent replacement of the LVAD system, which unfortunately gave only a temporary effect. On the 126th day the patient died. Also, one patient had an SCD event without a specific localization without a lethal consequence.

One patient receiving Warfarin monotherapy and had reoperation for chest bleeding in the first week of the postoperative period, an event of thrombosis of the pump engine of LVAD device (TPE), followed by LVAD replacement, renal and pulmonary insufficiency in a later period that has a fatal outcome.

The patient receiving Fondaparinux Na in combination with aspirin and warfarin had a nephrological event and a non-definite etiology and localization bleeding of the gastrointestinal tract during the first week.

The patient, who has, on the third day of heparin therapy, transferred to therapy, with Clopidogrel, received in the second week an event of ischemic damage to the brain.

Five patients who had combined ACTT with Warfarin, Aspirin, Clopidogrel in 30% had a GIB non-identified etiology and 20% of renal events.

Discussion. Bleeding is the most common development after LVAD implantation. Such patients need antiplatelet and anticoagulant therapy, which increases the likelihood of bleeding. The bleeding that occurs in the first 14 days after implantation is mainly due to surgical intervention. The reasons for later bleeding include the development of arteriovenous malformations, liver dysfunction from post-implantation right ventricular failure and acquired von Villebrand syndrome. Non-surgical, early bleeding to 30 days after implantation can occur in 20–40% of patients. Within six months after discharge, the number of cases of bleeding is about 13% [4]. Identifying the potential causes and risk factors for bleeding is important to improve the treatment outcomes and quality of life of patients with LVAD.

Gastrointestinal bleeding occurs on average after 33 days from surgery (range: from 1 to 530 days), with the highest risk during the first post-operative month. This is the most common cause of 30-day regasification [3]. The total risk of GI for patients receiving such varieties of left ventricular mechanical support devices as HeartMate II and HeartWare is 21%, 27% and 31% for one, three, and five years, respectively [5, 6]. In this case, the previous reports revealed that the upper gastrointestinal tract is the most common place of bleeding from the gastrointestinal tract in recipients of LVAD [5,7].

A recent small retrospective study found out that video-encapsulated endoscopy, which uses snapshot of an oral disposable micro camera to fix the gastrointestinal tract [6], is a safe and feasible way to explain incomprehensible GIB. Preferably, only the video assistant endoscopy revealed bleeding from the small intestine, in which no source or defect (50%) and angiodysplastic changes of the small intestine (33.3%) were detected. The diagnostic effect of the study was positive in 40% of patients. However, it was carried out on average six days after the correction of coagulopathy and after other endoscopic procedures, when it was not possible to detect the cause of an incomprehensible SQC [6].

Factors, contributing to GI can be associated with increased intra-abdominal pressure, which leads to the development of angiodysplasia of the gastrointestinal tract. Another possible explanation for the high incidence of CMV among recipients with laminar LVAD is the acquired fon Villebrand syndrome, which is a secondary phenomenon after hemolysis due to the high rotational motion of the motor, due to the subsequent splitting of the macromolecular multimers into the smaller ones that are filtered and released from the bloodstream, leading to loss or reduction of large von Villebrand factor multimers that are necessary to stimulate platelets [7]. Recent studies have shown that all patients have developed typical Laboratory results of acquired fon Villebrand syndrome (ASFV) after LVAD implantation, but not all have bleeding [8.9]. These data suggest that only NSAIDs are insufficient for the development of complications in bleeding after LVAD implantation.

Another serious complication is a hemorrhage in the central nervous system, which occurs relatively late. In a study with HeartMate II, the targeted therapy in the first two years after LVAD implantation showed a 11% risk of hemorrhagic stroke as a major factor in delayed lethality [10]. In a randomized study of 734 patients, a significantly higher incidence of hemorrhagic stroke was observed in patients receiving HeartWare compared to HeartMate II [5]. In a recent retrospective review of 114 patients with HeartMate II, 5% of them had intracranial hemorrhage [11]. Proportionally, more

patients taking 325 mg aspirin had hemorrhagic intracranial events compared to a group of patients who took aspirin at a dose of 81 mg in combination with dipyridamole, or simply aspirin at a dose of 81 mg. High doses of aspirin in patients with HeartMate II that are concurrently received warfarin, were associated with an increased risk of bleeding, but did not reduce thrombotic events [11].

An important cause of early regasification, after LVAD implantation, is anemia without a bleeding source that requires red blood cell transfusion and accounts for 20% of all bleeding [12].

Strategies for reducing the frequency and severity of complications such as bleeding include: lowering the norm of the international normalized ratio (INR), reducing the use of antiplatelet drugs, and adaptive motor speed correction to provide a pulsating flow.

A recent study showed that lower LV pulmonary implantation resulted in an increase in bleeding percentages. According to Waver-Pinzon O. et al., in patients with a low pulsation index the risk factor was 4.06 ($p = 0.04$) compared to the group where high pulsation indices were used [13].

The optimal treatment of a patient with an increased risk of bleeding remains impulsive and always heavily dependent on a combination of factors associated with the patient and the device. The patient's clinical condition often requires a temporary change in the INRs, often by reducing or temporarily discontinuing anticoagulation treatment to stop significant or even life-threatening bleeding. Boyle A.J. those co-operating with the LVAD Safety Study Corridor, concluded that a target INR of 1.5 to 2.5 (in addition to aspirin therapy) could be safe in patients with an increased risk of bleeding [14]. However, this benefit is due to a significantly higher risk of thrombotic events [15].

Despite antithrombotic treatment, thromboembolic events are common after LVAD implantation. These include: cerebrovascular ischemic event, transient ischemic attack, arterial embolism of the central nervous system, or thrombosis of the device engine.

Neurological events remain one of the most complicated complications after LVAD implantation and are often the main cause of fatal cases [14]. The indicated incidence of ischemic stroke during HeartMate II support as a heart transplant event and targeted therapy is 0.064-0.082 events per year of life of a patient with LVAD implanted [16]. The frequency of ischemic stroke, for HeartWare, was 0.11 events per patient year [4]. Multivariate analysis has shown that diabetes mellitus, the time of aortic compression during arterial blood circulation and higher INRs are independent predictors of stroke. According to Morgan JA, Brewer RJ et al. the mean INS at the time of stroke was sub-therapeutic in all patients with embolic stroke patients with diabetes were 6.36 times more likely to have a stroke than those who did not have a stroke [17]. Complete compression of the aorta with the use of cardioplegia, compared with partial lateral contractions, was associated with a significantly higher incidence of stroke and was an independent predictor of stroke [16].

Atrial fibrillation (AF) is a well-established risk factor for thromboembolic complications and is common in patients with severe heart failure, including LVAD implantation patients. However, a recent retrospective analysis of the INTERMACS data from primary LVADs suggests that preoperative AF does not increase the risk of postoperative thromboembolic complications or mortality during the interim period [18]. This indicates that the usual post-operative antithrombotic strategy most likely is also suitable for patients with AF that undergo LVAD implantation.

The incidence of TNDP three months after LVAD implantation increases unexpectedly from 2.2% to 8.4% after HeartMate II implantation [16], while the frequency of cardiac thrombosis remains stable. Thrombosis of the pump requiring replacement was observed in 4% of patients, and the overall morbidity and prevalence of TNDP was 0.08 PPR and 8.1% respectively [19].

In general, alternative anticoagulant targeted therapies have been proposed to prevent TNDPs. However, there is little evidence that supports any treatment scheme, which led to the study of this issue at the Silesian Center for Heart Disease.

A recent study aimed at evaluating outpatient treatment with warfarin showed that thrombotic events (TNDP and ischemic stroke suspects) were the highest among the lowest INRs (<1.5 [0.40 thrombotic PRP]), but the INRs were also 1.5 to 1.99. had high rates (0.16 thrombotic PRP) [14]. There is a lack of statistically significant association between INRs and thrombotic events in the time period from the time of implantation to three months after the LVAD implantation, indicating that the early TNDP can be caused by INR-independent events such as type of surgical intervention, type of device, type of postoperative anticoagulation bridge therapy [15]. On the contrary, after an early post-surgical period, intensive anticoagulation assumed TNDP. The results of their weighted analysis show that the target INR of 2.6 is optimal for avoiding both bleeding and thrombotic complications and also minimizing mortality [15]. These findings confirm the existing practice and convinced that the target

range of INRs from 2.0 to 3.0 minimizes all significant side effects, as evidenced by Nassif M.E. and all. [15].

In response to previous studies showing early TNDPs up to 8.4% in patients receiving HeartMate II, non-randomized, prospective, multicenter-simultaneous studies of anticoagulant therapy for the prevention of thrombosis of LVAD devices were submitted to a survey of 300 patients who were implanted in a LVAD device in 24 US Centers and who agreed to adhere to simple guidelines for outpatient treatment [21]. The study showed a 2.9% TNDP frequency three months after implantation and 4.8% in 6 months. As a result of the research, it was recommended to change the frequency of TNDPs to maintain the INR value within 2.0-2.5, to initiate early warfarin and aspirin therapy, to maintain optimal control of the rate (> 5000 rpm) and mean arterial pressure <90 mmHg

CONCLUSIONS

1. Hemorrhagic and ischemic stroke is one of the most difficult and prognostically adverse complications, and was manifested in 30% of the patients in the examined group.
2. An alternative ACCT using thrombin inhibitors, P1Y12 block, and aspirin in patients of the study group had an effect in which mortality and the number of complications associated with hemorrhagic and thromboembolic events were significantly lower.
3. The highest percentage of complications, in the form of bleeding of thromboembolic events, was in the control group of patients receiving monotherapy with heparin or warfarin or their combination.

Conflict of Interest: The authors do not foresee conflicts of interest.

REFERENCES

1. *Kirklin J.K., Naftel D.C., Pagani F.D., Kormos R.L., Stevenson L.W., Blume E.D., Myers S.L., Miller M.A., Baldwin J.T., Young J.B. Seventh INTERMACS annual report: 15,000 patients and counting. J. Heart. Lung. Transplant. 2015 Dec;34(12):1495-504.*
2. *Akhter S.A., Badami A., Murray M., Kohmoto T., Lozonschi L., Osaki S., Lushaj E.B. Hospital Readmissions After Continuous-Flow Left Ventricular Assist Device Implantation: Incidence, Causes, and Cost Analysis. Ann. Thorac. Surg. 2015 Sep;100(3):884-9.*
3. *Wever-Pinzon O., Drakos S.G., Kfoury A.G., Nativi J.N., Gilbert E.M., Everitt M., Alharethi R., Brunisholz K., Bader F.M., Li D.Y., Selzman C.H., Stehlik J. Morbidity and mortality in heart transplant candidates supported with mechanical circulatory support: is reappraisal of the current United network for organ sharing thoracic organ allocation policy justified? Circulation. 2013 Jan 29;127(4):452-62*
6. *Amornsawadwattana S., Nassif M., Raymer D., LaRue S., Chen C.H.. Video capsule endoscopy in left ventricular assist device recipients with obscure gastrointestinal bleeding. World J. Gastroenterol. 2016 May 14;22(18):4559-66.*
7. *Kushnir V.M., Sharma S., Ewald G.A., Seccombe J., Novak E., Wang I.W., Joseph S.M., Gyawali C.P.. Evaluation of GI bleeding after implantation of left ventricular assist device. Gastrointest Endosc. 2012 May;75(5):973-9.*
8. *Crow S., Chen D., Milano C., Thomas W., Joyce L., Piacentino V., Sharma R., Wu J., Arepally G., Bowles D., Rogers J., Villamizar-Ortiz N. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann. Thorac. Surg. 2010;90(4):1263-9.*
9. *Meyer A.L., Malehsa D., Bara C., Budde U., Slaughter M.S., Haverich A., Strueber M. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ. Heart Fail. 2010;3(6):675-81.*
10. *Slaughter M.S., Rogers J.G., Milano C.A., Russell S.D., Conte J.V., Feldman D., Sun B., Tatooles A.J., Delgado R.M., Long J.W., Wozniak T.C., Ghumman W., Farrar D.J., Frazier O.H. HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. N. Engl. J. Med. 2009 Dec 3;361(23):2241-51.*
11. *Saeed O., Shah A., Kargoli F., Madan S., Levin A.P., Patel S.R., Jermyn R., Guerrero C., Nguyen J., Sims D.B., Shin J., D'Alessandro D., Goldstein D.J., Jorde U.P. Antiplatelet Therapy and Adverse Hematologic Events During Heart Mate II Support. Circ Heart Fail. 2016 Jan;9(1):e002296.*
12. *Bunte M.C., Blackstone E.H., Thuita L., Fowler J., Joseph L., Ozaki A., Starling R.C., Smedira N.G., Mountis M.M. Major bleeding during HeartMate II support. J. Am. Coll. Cardiol. 2013 Dec 10;62(23):2188-96.*
13. *Wever-Pinzon O., Selzman C.H., Drakos S.G., Saidi A., Stoddard G.J., Gilbert E.M., Labedi M., Reid B.B., Davis E.S., Kfoury A.G., Li D.Y., Stehlik J., Bader F. Pulsatility and the risk of nonsurgical bleeding in patients supported with the continuous-flow left ventricular assist device HeartMate II. Circ Heart Fail. 2013 May;6(3):517-26.*
14. *Boyle A.J., Russell S.D., Teuteberg J.J., Slaughter M.S., Moazami N., Pagani F.D., Frazier O.H., Heatley G., Farrar D.J., John R. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J. Heart Lung. Transplant. 2009 Sep;28(9):881-7.*
15. *Nassif M.E., LaRue S.J., Raymer D.S., Novak E., Vader J.M., Ewald G.A., Gage B.F. Relationship Between Anticoagulation Intensity and Thrombotic or Bleeding Outcomes Among Outpatients With Continuous-Flow Left Ventricular Assist Devices. Circ. Heart Fail. 2016 May;9(5).*
16. *Harvey L., Holley C., Roy S.S., Eckman P., Cogswell R., Liao K., John R. Stroke After Left Ventricular Assist Device Implantation: Outcomes in the Continuous-Flow Era. Ann. Thorac. Surg. 2015;100(2):535-41.*
17. *Morgan J.A., Brewer R.J., Nemeh H.W., Gerlach B., Lanfear D.E., Williams C.T., Paone G. Stroke while on long-term left ventricular assist device support: incidence, outcome, and predictors. ASAIO J. 2014 May-Jun;60(3):284-9.*
18. *Xia Y., Stern D., Friedmann P., Goldstein D.. Preoperative atrial fibrillation may not increase thromboembolic events in left ventricular assist device recipients on midterm follow-up. J. Heart. Lung. Transplant. 2016;35(7):906-12.*
19. *Najjar S.S., Slaughter M.S., Pagani F.D., Starling R.C., McGee E.C., Eckman P., Tatooles A.J., Moazami N., Kormos R.L., Hathaway D.R., Najarian K.B., Bhat G., Aaronson K.D., Boyce S.W.; HVAD Bridge to Transplant ADVANCE Trial Investigators. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J. Heart Lung. Transplant. 2014 Jan;33(1):23-34.*
20. *Uriel N., Morrison K.A., Garan A.R., Kato T.S., Yuzefpolskaya M., Latif F., Restaino S.W., Mancini D.M., Flannery M., Takayama H., John R., Colombo P.C., Naka Y., Jorde U.P.. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. J. Am. Coll. Cardiol. 2012 Oct 30;60(18):1764-75.*
21. *Maltais S., Kilic A., Nathan S., Keebler M., Emani S., Ransom J., Katz J.N., Sheridan B., Brieke A., Egnaczyk J., Entwistle J.W., Adamson R., Stulak J., Uriel N., O'Connell J.B., Farrar D.J., Sundareswaran K.S., Gregoric I. PREVENTion of HeartMate II Pump Thrombosis Through Clinical Management (PREVENT). J. Heart Lung. Transplant. 2016;35(4):S161-S162.*
22. *Starling R.C., Moazami N., Silvestry S.C., Ewald G., Rogers J.G., Milano C.A., Rame J.E., Acker M.A., Blackstone E.H., Ehrlinger J., Thuita L., Mountis M.M., Soltesz E.G., Lytle B.W., Smedira N.G. Unexpected abrupt increase in left ventricular assist device thrombosis. N. Engl. J. Med. 2014;370(1):33-40.*
23. *Saeed D., Maxhera B., Albert A., Westenfeld R., Hoffmann T., Lichtenberg A. Conservative approaches for HeartWare ventricular assist device pump thrombosis may improve the outcome compared with immediate surgical approaches. Interact. Cardiovasc. Thorac. Surg. 2016;23(1):90-5.*
24. *Mandeep R. Mehra, M.D., Daniel J. Goldstein, M.D., Nir Uriel, M.D., Joseph C. Cleveland, Jr., M.D.et al.,for the MOMENTUM 3 Investigators "Two-Year Outcomes with Magnetically Levitated Cardiac Pump in Heart Failure." New England Journal of Medicine. IE.*