

# Argatroban administration as therapy for thrombosis in patients with continuous-flow ventricular assist devices

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**Background:** Device thrombosis is one of the main complications in left ventricular assist devices (LVAD) therapy and remains a challenging issue. Data on device thrombosis management, especially on the application of direct thrombin inhibitors such as argatroban, is limited and a consensus on thrombosis management has not yet been established.

**Methods:** In this study we analysed retrospective clinical data obtained from 26 patients on VAD therapy who received argatroban for suspected VAD thrombosis, between April, 2012 and February, 2017.

**Results:** Thirteen patients (50%) showed resolution of thrombus after argatroban therapy. Eight of 26 patients (30.8%) were free of thrombotic events 90 days after discharge. Argatroban therapy was unsuccessful in 13 patients of the study cohort, leading to subsequent VAD-exchange. Six of 13 patients with first VAD-exchange had no thrombotic events 90 days after discharge. Six patients (23.1%) suffered from bleeding, especially gastrointestinal bleeding. No hemorrhagic strokes were observed. Three patients (11.5%) did not survive the follow-up period.

**Conclusions:** Argatroban appears to be an alternative to other pharmacological treatment options in VAD thrombosis. Efficacy and safety characteristics are acceptable, but further investigation on larger populations is necessary.

**Keywords:** Left ventricular assist device (LVAD); VAD thrombosis; argatroban; anticoagulation; lysis

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## Introduction

Left ventricular assist devices (LVAD) have improved the survival rates of patients with terminal heart failure and can be implanted to bridge patients to heart transplantation or to improve the symptoms of patients ineligible for transplantation (1-5). Currently implantation, exchange and explantation of VAD-systems can be minimally invasive, in order to reduce trauma and infection (6-10). Complications of device therapy are common and can include thrombotic

and bleeding complications (11-13). Recent registry data show that up to 70% of patients will have a major complication during the first year of device support (14). Risk factors for developing device thrombosis have been identified as pump-specific such as shear stress, flow dynamics and blood trauma, as well as patient-dependent [e.g., atrial fibrillation, pre-existing atrial or ventricular thrombus, non-compliance, hypercoagulable disorders (15)], implantation technique and anticoagulation strategies (16). Typical clinical symptoms include increased pump power, anemia, recurrent

**Table 1** Baseline characteristics of the study cohort

Characteristic	N=26
Sex	
Male	19 (73.1)
Female	7 (26.9)
Age, years	57.7±10.4
Cardiomyopathy	
Dilated cardiomyopathy	16 (61.5)
Ischemic cardiomyopathy	6 (23.1)
Hypertrophic non-obstructive cardiomyopathy	1 (3.8)
Peripartum cardiomyopathy	1 (3.8)
Toxic cardiomyopathy	1 (3.8)
Device	
HVAD	20 (76.9)
HM II	2 (7.7)
HM3	1 (3.8)
HA5	2 (7.7)
MVAD	1 (3.8)
Days on support from first implantation until pump thrombosis	1,398.54±772.64
INR, 2.0–3.0	13 (50.0)

Data are presented as mean ± standard deviation (SD) or n (%). HVAD, HeartWare ventricular assist device; HM, HeartMate; MVAD, miniaturized ventricular assist device; INR, international normalization ratio.

heart failure and hemolysis (17). LVAD thrombosis may be confirmed by echocardiography (18), computed tomography (CT) (19) or cardiac catheterization (20). The recommended treatment of LVAD thrombosis is pump replacement or emergency heart transplantation (16,21).

Conservative thrombosis management involves intravenous (IV) therapy with heparin (15). However, the reported mortality rate of patients treated medically is 50% (22). Hence there is critical need for new strategies for LVAD patient anticoagulation management. Previously published case series have suggested the application of glycoprotein (GP)-inhibitors for suspected device obstruction (23–26), which was associated with excessive bleeding events. Investigators concluded that the risk of

medical therapy with eptifibatide outweighed the benefits of GP-inhibitor application (26). Data on the application of direct thrombin inhibitors such as argatroban and bivalirudin is limited. Argatroban is a direct reversible thrombin inhibitor that interacts with free and clot-bound thrombin and inhibits the activation of coagulation factors V, VIII, XIII and protein C (27). Preliminary data from previously published case series on treating patients with device-related thrombosis with argatroban is promising (28).

The purpose of the current study was to investigate the safety and effectiveness of argatroban therapy for device-related thrombosis as an alternative to pump exchange.

## Methods

### *Clinical data acquisition*

Data was collected by electronic medical record review. In this retrospective study 26 patients on VAD-therapy have been included who were admitted to our outpatient clinic between April, 2012 and February, 2017 with suspected VAD-thrombosis. Nineteen patients were on HeartWare ventricular assist device (HVAD) support, three on HeartMate II (HM II), two on HeartAssist 5 (HA5) and one on HeartMate 3 (HM3) and miniaturized ventricular assist device (MVAD). These patients were subsequently hospitalized and treated with argatroban. Criteria for suspected VAD-thrombosis were defined as either hemolysis or altered VAD-parameters, such as change in flow or motor power. Data collected until February 28<sup>th</sup> 2017 was analyzed for this study. All adverse events were determined through retrospective examination of medical records.

### *Argatroban administration*

The argatroban dosage was started as a permanent IV infusion (2 µg/kg/min) at admission.

### *Statistical analysis*

SPSS 23.0 package (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis of clinical data. Categorical and continuous variables were summarized as frequencies, percentages and mean/median with interquartile range, respectively. The student's *t*-test was applied to compare baseline characteristics of inpatient admission and discharge with statistical significance considered for  $P < 0.05$ .

**Table 2** Laboratory parameters before and after in-patient stay

Laboratory parameters	Admission	Discharge	P value
aPTT, s	49.8±11.6	50.7±19.8	0.419
Plasma-free Hb, mg/L	1,031.3±1,311.1	83.3±63.6	<0.05
Serum-GOT, U/L	142.0±130.0	31.8±15.6	<0.05
Serum-GPT, U/L	45.3±67.2	26.6±13.0	0.070
Serum-Urea, mmol/L	9.6±8.6	10.2±9.1	0.396
INR	2.5±0.7	2.4±0.5	0.221
Serum-Creatinine, µmol/L	129.3±70.5	169.7±135.9	<0.05
Plasma-Lactate, mmol/L	1.7±1.0	1.3±0.6	<0.05
Serum-Lactate dehydrogenase, U/L	1524.0±1175.1	437.3±202.5	<0.05
Serum-NT-proBNP, ng/L	1,878.1±3,322.6	2,523.3±5,908.7	0.155
Thrombocytes, 10 <sup>9</sup> /µL	220,076±89,598	300,884±117,458	<0.05
Urin test strip, hematuria, positive (%)	17* (65)	**	

Data are presented as mean ± standard deviation (SD). \*, indicates data collected from 19 patients; \*\*, indicates no data.

**Table 3** VAD parameters before and after in-patient stay.

VAD parameters	Admission	Discharge	P
Speed, U/min	4,231.5±2,945.5	4,118.8±2,458.0	0.386
Flow, L/min	6.3±3.2	5.1±1.0	<0.05
Motor power, W	6.4±3.0	4.9±0.9	<0.05

Data are presented as mean ± standard deviation (SD). VAD, ventricular assist device.

## Results

### *Patient profile prior to argatroban administration*

Data from 26 patients with suspected pump thrombosis, who were treated with argatroban between April, 2012 and February, 2017 was analyzed in this study. Detailed baseline characteristics of the study group can be found in *Table 1*. In 73.1% of the study population was male, with a mean age of 57.7 years. In 61.5% of the study group dilated cardiomyopathy was the primary heart disease prior to LVAD implantation. In 23.1% ischemic cardiomyopathy and in 3.8% hypertrophic, non-obstructive, peripartur or toxic cardiomyopathy was the underlying disease. Mean duration of support when treated with argatroban for pump thrombosis was 1,398 days. Fifty percent of the patients in the current study exhibited deranged international normalization ratio (INR) at the time of hospital admission.

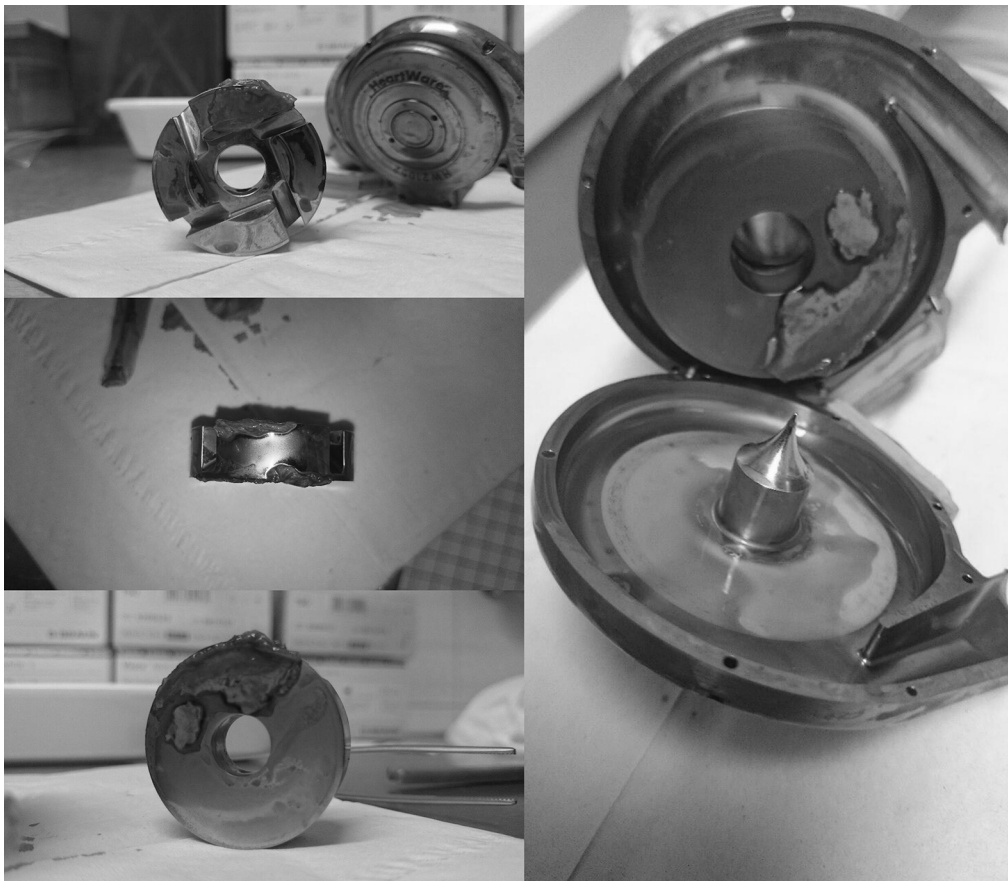
Laboratory values at the time of admission and discharge

are listed in *Table 2*. Serum levels of free hemoglobin (fHb), glutamic-oxaloacetic transaminase (GOT), lactate and lactate dehydrogenase (LDH) at the time of admission were elevated. At the time of discharge fHb, GOT, lactate and LDH levels were significantly decreased. Furthermore, thrombocyte and creatinine level in patients were significantly higher at discharge. In 65% of the patients displayed hematuria upon hospitalization.

VAD-parameters such as flow and motor power appeared to significantly rise at the time of admission (*Table 3*).

### *Clinical outcome after argatroban therapy due to pump thrombosis*

Thirteen patients (50%) displayed normalization of clinical symptoms, laboratory values and VAD-parameters, upon argatroban therapy. These 13 patients did not require further intervention and were discharged. In 5 of 13 patients



**Figure 1** Explanted and disassembled HVAD pump. Exposed thrombus between front housing and impeller. HVAD, HeartWare ventricular assist device.

**Table 4** Adverse events observed in the study cohort

Adverse event	Number of patients, n (%)
Bleeding	6 (23.1)
Gastrointestinal	4 (15.4)
Epistaxis	2 (7.7)
Cerebral hemorrhage	1 (3.8)
Intraoperative at pump exchange	13 (50.0)
Stroke	4 (15.4)
Cardiac transplantation	2 (7.7)
Death	3 (11.5)

recurrent thrombosis occurred after a mean duration of 217 days (minimum 30 days, maximum 648 days). Three patients displaying such recurrent thrombosis were successfully treated with argatroban therapy. In two patients

VAD exchange was necessary. One patient developed re-thrombosis 7 days after the VAD exchange and received cardiac transplant (*Figure 1*). Eight of 13 patients (30.8%) remained free from pump thrombosis.

In the other 13 patients of the study cohort argatroban therapy failed and an exchange of the VAD-system was performed. In 26.9% of those patients developed re-thrombosis on an average of 255 days (range 14–760 days) later. In 5 patients re-thrombosis could be treated successfully with argatroban, in one patient the VAD system had to be changed again and one patient successfully received cardiac transplant. 90 days after discharge 6 of 13 patients with first VAD-exchange (23.1%) remained free of pump thrombosis (*Figure 2*).

#### *Adverse events*

All observed adverse events are listed in *Table 4*. Four of

all patients (15.4%) had a stroke event during the follow up period. In 11.5% the stroke occurred during the postoperative course after VAD-exchange. Hemorrhagic strokes were not observed.

Six patients of the study cohort (23.1%) had bleeding events after argatroban therapy. One patient displayed gastrointestinal bleeding six months after argatroban therapy, and needed blood transfusion. Another patient had to be re-hospitalized due to gastrointestinal bleeding only four days after discharge. This patient developed epistaxis and two major gastrointestinal bleedings during the next three months. One patient experienced five episodes of gastrointestinal bleeding, four months after therapy with argatroban. Another patient required electrocoagulation for epistaxis ten days after argatroban therapy and VAD-exchange. One patient suffered an ischemic stroke, followed by a hemorrhage 19 months after argatroban therapy.

In all patients requiring VAD-exchange due to insufficient argatroban therapy, intraoperative substitution of erythrocytes (mean of four erythrocyte concentrates) was necessary.

In total two patients have been listed for high urgency heart transplantation. One patient was transplanted due to a recurrent thrombosis after first VAD-exchange. In this patient argatroban showed both times no effect. The other heart transplanted patient was initially treated successfully with argatroban. However, the argatroban treatment of the re-thrombosis failed this time and the patient received a VAD-exchange. After the third re-thrombosis the patient has been successfully transplanted.

During the observation period 11.5% patients died. In the study population the main causes of death were multi-organ failure (3.8%) and ischemic stroke (3.8%). The cause of death of another patient is unknown.

## Discussion

Pump thrombosis is a severe, life threatening complication of VAD-therapy. The gold standard for VAD thrombosis therapy is heart transplantation. Due to low availability of donor organs, the common therapy is VAD exchange (29,30). Due to perioperative complications, conservative treatment of VAD-thrombosis is an alternative option. Despite this limited data is available for alternative therapeutic strategies.

This study is the first to evaluate argatroban administration for therapy of suspected VAD-thrombosis. In our study cohort a change of VAD-parameters, laboratory

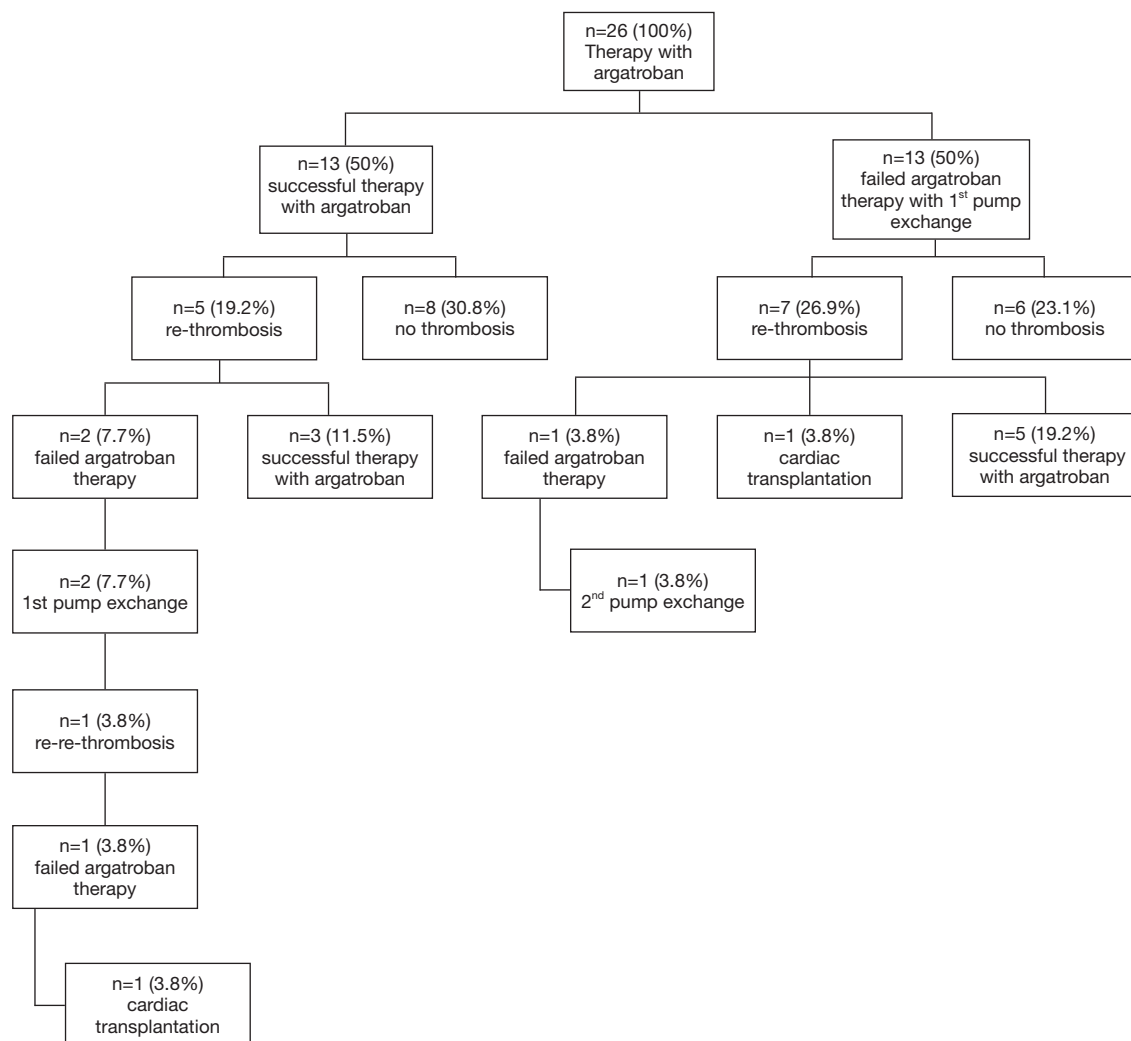
values or clinical symptoms were inclusion criteria. Laboratory analyses revealed elevated levels of LDH, fHb, GOT and lactate at the time of hospital admission. Sixty-five percent of the patients also had hemoglobinuria. At the time of hospital discharge a significant decrease of all parameters was observed. Elevation at the time of admission is due to shear forces at the thrombus with destruction of erythrocytes. Decrease at discharge can be seen as result of a successful resolution of the thrombus. Further on thrombocytes and serum-creatinin-level showed to be elevated at the time of discharge. Argatroban is hepatically metabolized and has no effect on kidney function. Most patients receive a lot of concurrent medication (e.g., analgesics). This could explain the increase in serum creatinine levels during hospitalization.

Furthermore, a change in pump parameters, such as an increase in motor power and a decrease in pump flow, are indirect signs of pump thrombosis. In our study cohort motor power and pump flow were significantly elevated at admission. Rise in motor power could be a consequence of a pump thrombosis, but a rise in pump flow cannot be explained by a thrombotic event. Pump parameters of six patients were missing at the time of hospital discharge, confounding the results.

With the results of this study we could show, that 50% of the patients, treated with argatroban for pump thrombosis, showed a successful resolution of the thrombus and 30.8% were free of a thrombotic event for a long post-operative follow-up period (80–1,504 days after discharge). Out of the patient cohort, which needed a VAD exchange due to insufficient argatroban therapy, only 23.1% were free of thrombosis for a long term (80–1,504 days after discharge).

There is a dearth of literature on argatroban therapy for pump thrombosis making it challenging to provide a comprehensive comparison of the data from this study with previous literature. In a case series with four patients Badiye *et al.* could show a successful resolution of the thrombus in three patients (28). Stulak *et al.* reported a successful medical treatment of pump thrombosis with tissue plasminogen activator, heparin or heparin and GP IIb/IIIa inhibitor of 48% (31). Only 21% patients of the study did not display re-thrombosis for 30 days (31). Other studies show an even lower rate of success for conservative therapy in pump thrombosis. Eptifibatide has been shown to successfully resolve pump thrombus in 17–22% (26). New data on tissue plasminogen activator is promising, indicating successful treatment in pump thrombosis of 66% (32).

The most common complications of a thrombolytic



**Figure 2** Flow chart depicting successful therapy of pump thrombosis with argatroban administration.

therapy are bleeding events. Hemorrhagic stroke is an especially debilitating adverse complication of thrombosis. In our study group 23.1% of all patients displayed bleeding events after argatroban therapy. Hemorrhagic strokes were not observed in our patient cohort and the most commonly observed complications were gastrointestinal bleedings, 11.5% of all patients died during the follow up period, but none because of bleeding events. In studies with eptifibatide authors reported a bleeding event rate of 64.7% and a rate of intraparenchymal hemorrhage as cause of death of 41% (26). Schrage *et al.* reported a rate of bleeding events for tissue plasminogen activator of 6%, but it has to be considered that the study cohort consisted of only nine patients (32). In another study medical treatment of pump thrombosis with tissue plasminogen activator,

heparin or heparin and GP IIb/IIIa inhibitor has shown to cause hemorrhage in 21% and death in 10% patients (31). Therefore, in comparison with the other available conservative therapeutic agents argatroban seems to be a promising option.

Without device explantation diagnosis of pump thrombosis can only be suspected and not verified. Additionally different studies on conservative treatment of pump thrombosis were performed on different VAD systems. In our study cohort most of the patients were on a HVAD system, but patients with HM II, HM3, HA5 and MVAD have also been included. Whether there is a direct correlation between a particular pump type and pump thrombosis has not yet been established (32). Patient specific characteristics also play an important role

in development of pump thrombosis (33). This makes the comparison of the different studies difficult and subject to potential bias.

### Limitations of the study

This study has some limitations. The data was retrospectively collected and analyzed and therefore is subject to the limitations associated with retrospective studies. All exchange procedures were performed at one institution and therefore may be affected by institutional experience. The study cohort with 26 patients is rather small, and could lead to an under- or overestimation of our results.

### Conclusions

In comparison with the other available conservative therapeutic agents argatroban appears to be a promising and safe option for patients with VAD-thrombosis. Further studies on a bigger study population are therefore required to evaluate the effectiveness and safety of argatroban administration as therapeutic agent in pump thrombosis.

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### Footnote

*Conflicts of Interest:* JD Schmitto and G Dogan are consultants of Medtronic Corporation. JD Schmitto receives consultation fees and financial grants from Abbott Laboratories. The other authors have no conflicts of interest to declare.

*Ethical Statement:* This retrospective study was approved by the ethics committee of the Hannover Medical School (Application number = 2204:2014).

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