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Increased Thromboembolic Events With Dabigatran Compared With Vitamin K Antagonism in Left Ventricular Assist Device Patients

A Randomized Controlled Pilot Trial

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Background—Left ventricular assist device–supported patients are usually anticoagulated with a combination of aspirin and vitamin K antagonists. Long-term vitamin K antagonist therapy can be complicated by unstable international normalized ratio values and patient-related compliance problems. Therefore, direct thrombin inhibitors may represent an alternative to vitamin K antagonists.

Methods and Results—Thirty HeartWare ventricular assist device patients with stable renal function were planned for this prospective, randomized, open-label, single-center study. Patients were randomized to receive either phenprocoumon or dabigatran in addition to aspirin for long-term anticoagulation. Treatment duration was scheduled for 1 year and stopped after observation of a primary end point. Dabigatran dose was 110 and 75 mg BID in patients with normal or impaired renal function (glomerular filtration rate >80 mL/min or between 80 and 30 mL/min, respectively). The study was stopped prematurely for safety reasons after 16 patients (61±8 years, 1 female) were randomized. Thromboembolic events occurred in 4 subjects receiving dabigatran (50%) and in 1 receiving phenprocoumon (13%; $P=0.28$). No major bleeding was recorded, and no patient died during the study. Median time to treatment termination was significantly shorter in dabigatran patients (8.5 versus 12.0 months; $P=0.015$).

Conclusions—Thromboembolic events on dabigatran led to early termination of a randomized controlled trial of dabigatran versus phenprocoumon in left ventricular assist device patients.

Clinical Trial Registration—<https://www.clinicaltrials.gov>. Unique identifier: NCT02872649.

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Key Words: anticoagulants ■ aspirin ■ dabigatran ■ glomerular filtration rate ■ hemorrhage

Left ventricular assist device (LVAD) therapy significantly improves hemodynamic stability, exercise capacity, and pulmonary hypertension. The ReVOLVE registry trial (Registry to Evaluate the HeartWare Left Ventricular Assist System) demonstrated excellent overall survival.¹ However, blood contact with foreign surfaces and turbulent flow patterns impose a significant risk of thromboembolism.^{2,3} Therefore, patients in most centers currently receive a dual antithrombotic therapy for outpatient care consisting of an antiplatelet agent together with a vitamin K antagonist.⁴ This therapy requires repetitive testing for international normalized ratio levels and is associated with bleeding and

thromboembolic complications.^{5,6} The event rate per patient-year for bleeding (excluding gastrointestinal), gastrointestinal bleeding, or stroke is ≈0.40, 0.06, and 0.08, respectively.¹ Only 30% of patients are without bleeding or thromboembolic complications after 1 year.⁷

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New oral anticoagulants may serve as an alternative to vitamin K antagonists for LVAD patients. Potential benefits might be a reduction of laboratory assessments and a stable anticoagulant effect. Dabigatran etexilate acts as a direct, reversible

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thrombin inhibitor and is approved for the prevention of postoperative venous thromboembolism after hip or knee surgery⁸ and for stroke prevention in patients with atrial fibrillation.⁹ The therapeutic effect of dabigatran was shown in noninferiority trials with enoxaparin.^{10,11} In addition, beneficial effects comparable to warfarin for the prevention of stroke in chronic atrial fibrillation and as anticoagulation after venous thromboembolism were reported.^{9,12} However, after initiation of this clinical trial, dabigatran failed to demonstrate safety in patients with mechanical heart valves.¹³ The thrombin clotting time was proven to be the most sensitive routine parameter used to measure the therapeutic effect of dabigatran.^{14,15} The current trial was designed to assess safety and tolerability of dabigatran etexilate in stable patients after LVAD implantation.

Methods

We performed a randomized, open-label, balanced parallel group, single-center, pilot clinical trial. The local Ethics Committee and the national competent authority approved this trial (EudraCT 2010-024534-38). Thirty patients with stable renal function after HeartWare ventricular assist device (HVAD) implantation were planned to receive the vitamin K antagonist phenprocoumon (Marcoumar, Meda Pharma GmbH, Bad Homburg, Germany) or dabigatran (Boehringer Ingelheim Pharma KG, Ingelheim, Germany) for long-term anticoagulation. HVAD patients were screened for study eligibility in a stable postoperative condition. Inclusion criteria were LVAD (HVAD, HeartWare Inc, Framingham, MA) implantation >1 month ago, stable renal function, age 18 years or older, and the ability to give informed consent. Patients were excluded from this trial if they had severe chronic renal impairment (creatinine clearance [CRCL] <30 mL/min [MDRD (Modification of Diet in Renal Disease) formula]), a history of a major thromboembolic or bleeding event, a significant bleeding disorder, HIV or hepatitis C infection, heparin-induced thrombocytopenia, or hypersensitivity to dabigatran or phenprocoumon.

Clinical outpatient visits were scheduled 2 weeks, 2 months, 4 months, 6 months, 9 months, and 12 months after inclusion. Study data were prospectively collected. Patients remained in the trial for 1 year unless a study-defined end point occurred. All adverse events were recorded according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) categories.¹⁶ Main outcome parameters were the number of major (life threatening or leading to chronic disability) and minor adverse events because of thromboembolic complications, the number of major and minor bleeding events (INTERMACS definition¹⁶), and the number of patients with necessary treatment changes. Additional outcome parameters were an increase of liver enzymes >3× upper limit and the treatment effects on coagulation parameters. The individual treatment duration of 1 year was discontinued early after a clinically relevant bleeding or thromboembolic episode or if transplantation was performed. Transplantation itself was not regarded as an adverse event, but individual follow-up was truncated thereafter. Premature study termination was prespecified in case of >40% early study terminations in the dabigatran group.

The implantation was performed in a minimally invasive approach when feasible as previously described or via full sternotomy.¹⁷ Early postoperative anticoagulation therapy was initiated with low-molecular-weight heparin and changed to phenprocoumon thereafter.¹⁸ Antithrombotic therapy was added with acetylsalicylic acid (200 mg/d) in accordance with the institutional protocol.

After randomization, phenprocoumon was continued in the control group and discontinued in patients randomized to dabigatran. Phenprocoumon dose was self-adjusted according to daily measured international normalized ratio levels with a target between 2 and 2.5. Dabigatran target dose was 110 mg dabigatran twice daily for patients with a normal renal function.⁹ Patients with an impaired renal function (CRCL >30 to <80 mL/min) received 75 mg twice daily.¹⁹

Descriptive statistical methods were applied to depict the study population on risk factors, operative characteristics, and outcome. Continuous variables were presented as mean and SD and compared

with the independent samples *t* test between study groups. Total numbers and proportions were reported for categorical outcomes and compared with the Fisher exact test. The Kaplan–Meier method with a log-rank test was performed to compare event-free survival (no adverse event leading to study termination or death) and adverse events. The life table method with a Wilcoxon–Gehan test was used to calculate median time to study termination. IBM SPSS Statistics 21 (IBM Corp; Released 2012; IBM SPSS Statistics for Mac, Version 21.0, Armonk, NY) was used for statistical analysis. A *P* value <0.05 was considered as significant.

Results

Preoperative and operative patient characteristics except for the INTERMACS level were comparable between groups (Table 1; Table I in the [Data Supplement](#)). Study groups were comparable about time on device, renal function, liver function, coagulation parameters, and pump characteristics (Table 1). Two patients received the full dose (110 mg BID), and 6 patients received the reduced dose (75 mg BID) of dabigatran. International normalized ratio was higher and thrombin clotting time lower in the phenprocoumon group (Table 2; Figure 1A and 1B). All but 1 patient had stable sinus rhythm during the study period.

The study was stopped prematurely because of safety concerns after the enrollment of 16 patients. Predefined end points leading to study termination occurred in 6 dabigatran patients (75%, 4 thromboembolic events and 2 transplantations) and in 1 phenprocoumon patient (12.5%, 1 thromboembolic event; Figure 2; *P*=0.041). The median time to treatment termination was significantly shorter in dabigatran patients (8.5 versus 12.0 months; *P*=0.015). Thromboembolic events occurred in 4 subjects receiving dabigatran (50%), which consisted of 3 pump thrombosis and 1 transient ischemic attack (Figure 3). However, the patient who experienced a transient ischemic attack during the study period also developed a pump thrombus early after study termination and switching to phenprocoumon, which may have developed already before dabigatran cessation. One patient who received phenprocoumon and had intermittent atrial fibrillation also had a pump thrombosis.

All patients with pump thrombosis were primarily treated with intravenous alteplase according to the current recommendations.^{20,21} No pump exchange was required in these patients. No other INTERMACS-defined adverse events occurred (including bleeding episodes), and no patient died during the observation period. Liver parameter, renal function, and pump readings were comparable between groups after 12 months (Table 2). In addition to the predefined study end points, the early poststudy period was also analyzed on the amount of required blood transfusions during eventual transplantation (compared with transplantations on dabigatran during the study) and poststudy survival. Perioperative blood transfusion during transplantation was high but did not differ between patients on dabigatran or on phenprocoumon (1950±1485 versus 2040±493 mL; *P*=0.90). Kaplan–Meier analysis of event-free survival, including the poststudy switching period, revealed a significantly increased risk in the dabigatran group because of 1 additional fatal cranial hemorrhage early after switching from dabigatran to phenprocoumon (Figure 3; *P*=0.017).

Table 1. Preoperative Patient Characteristics and Patient Characteristics at Randomization

	Dabigatran (n=8)	Phenprocoumon (n=8)	P Value
Preoperative patient characteristics			
Age, y	61±6	64±9	0.35
Sex, f/m	0 (0%)/8 (100%)	1 (12.5%)/7 (87.5%)	1.00
Height, cm	178±6	173±11	0.34
Weight, kg	88±11	81±15	0.29
Body mass index, kg/m ²	27.9±3.1	26.7±3.1	0.47
INTERMACS level			
Level 1	0 (0%)	5 (62.5%)	
Level 2	3 (37.5%)	2 (25%)	
Level 3	3 (37.5%)	0 (0%)	
Levels 4–6	2 (25%)	1 (12.5%)	
Ischemic CMP	3 (37.5%)	5 (62.5%)	
Dilative CMP	5 (62.5%)	3 (37.5%)	
EuroSCORE II, %	19.6±22.8	31.0±21.5	0.38
Ejection fraction, %	15.4±4.2	11.9±4.6	0.15
Previous smokers	6 (75%)	4 (50%)	0.61
Diabetes mellitus	3 (37.5%)	1 (12.5%)	0.57
Dyslipidemia	5 (62.5%)	5 (62.5%)	1.00
Functional parameter at inclusion			
NYHA level			
NYHA I	3 (37.5%)	1 (12.5%)	0.57
NYHA II	5 (62.5%)	7 (87.5%)	
NYHA III	0 (0%)	0 (0%)	
NYHA IV	0 (0%)	0 (0%)	
Time from LVAD implant, d	298±186	475±360	0.24
Blood pressure, mm Hg	87±7.5	84±3.5	0.34
Creatinine, mg/dL	1.3±0.3	1.2±0.3	0.44
GFR (MDRD), mL min ⁻¹ kg ⁻¹	56.61±13.21	62.48±18.50	0.48
Liver profile			
ASAT/SGOT, U/L	29±10	27±12	0.66
GGT, U/L	71±56	54±47	0.51
LDH, U/L	234±38	214±36	0.29
Pump parameters			
Flow, L	5.7±1.2	5.3±0.5	0.40
Power, W	4.2±0.9	4.4±0.7	0.76
Speed, RPM	2720±195	2755±116	0.67

Continuous data are presented as the mean and SD; categorical data as total number and percentage. ASAT indicates aspartate aminotransferase; CMP, cardiomyopathy; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LDH, lactate dehydrogenase; LVAD, left ventricular assist device; MDRD, Modification of Diet in Renal Disease study equation; NYHA, New York Heart Association; RPM, round per minute; and SGOT, serum glutamic-oxaloacetic transaminase.

Table 2. Laboratory Values at 12 Months Follow-Up

Factor	Dabigatran (n=8)	Phenprocoumon (n=8)	P Value
Creatinine, mg/dL	1.6±0.3	1.3±0.4	0.31
GFR (MDRD), mL min ⁻¹ kg ⁻¹	45.08±10.78	59.34±18.34	0.34
Thrombin clotting time, s	112.6±6.5	15.1±2.0	<0.01
INR	1.6±0.1	3.4±1.1	0.06
Liver profile			
ASAT/SGOT, U/L	34±17	27±10	0.46
GGT, U/L	35±11	58±53	0.58
LDH, U/L	139±127	219±36	0.14
Pump parameters			
Flow, L	5.7±1.2	5.3±0.5	0.40
Power, W	4.2±0.9	4.4±0.7	0.76
Speed, RPM	2850±71	2725±117	0.22

Continuous data are presented as the mean and SD. ASAT indicates aspartate aminotransferase; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; LDH, lactate dehydrogenase; MDRD, Modification of Diet in Renal Disease study equation; and RPM, round per minute.

Discussion

This is the first randomized controlled trial assessing an alternative to vitamin K antagonists for long-term anticoagulation after LVAD implantation. It was designed in 2010, when the first multicenter clinical trials reported favorable results for

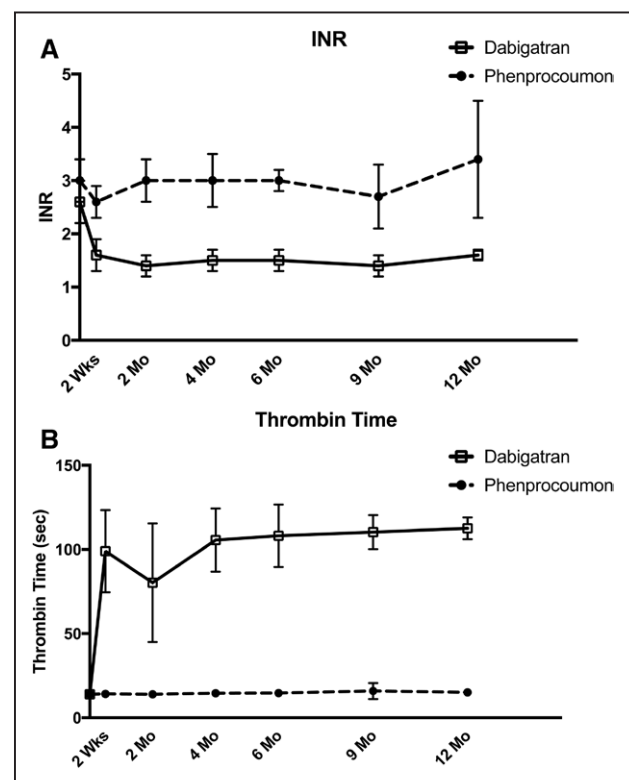


Figure 1. International normalized ratio (INR) and thrombin clotting time during the study period. **A**, INR for the dabigatran and phenprocoumon groups. **B**, Thrombin clotting time for the dabigatran and phenprocoumon groups.

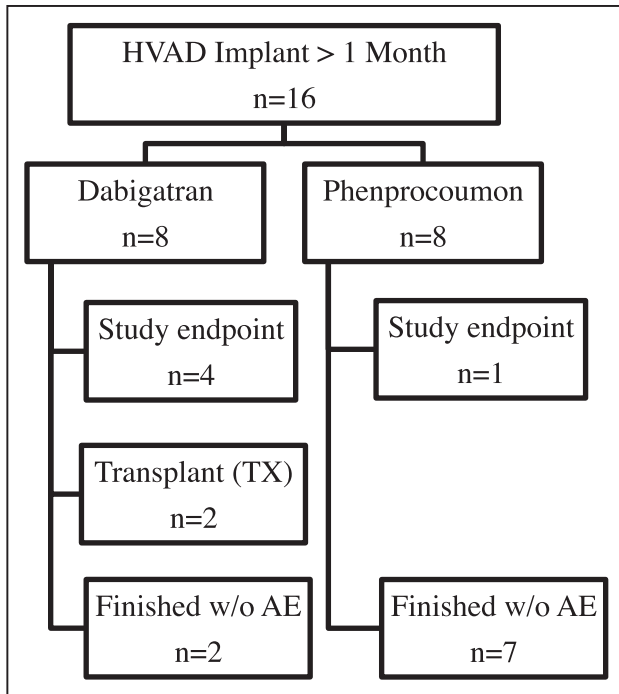


Figure 2. Flowchart of enrolled patients (n=16). Study end point was because of adverse event (pump thrombosis). AE indicates adverse event; and TX, cardiac transplantation.

dabigatran before the publication of the negative trial on dabigatran for antithrombotic therapy in patients with mechanical heart valves in 2013 (RE-ALIGN [Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement]).¹³ Implications of the RE-ALIGN study for this trial were discussed in detail. The study team decided to continue this trial in

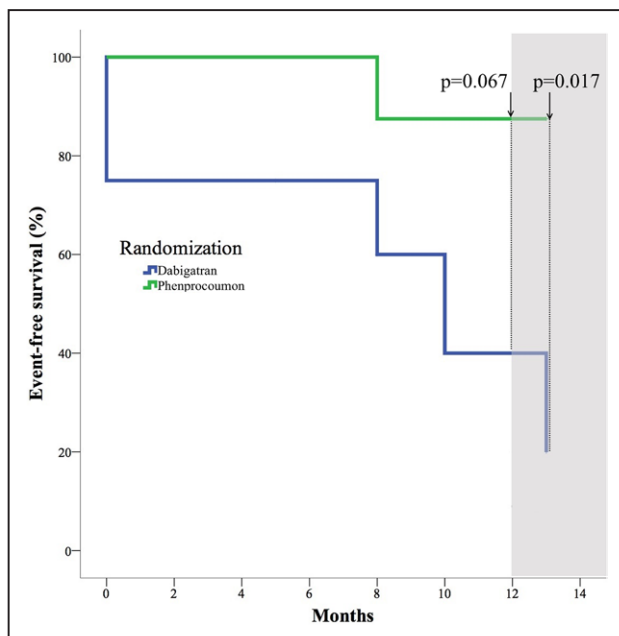


Figure 3. Kaplan–Meier analysis of event-free survival. Event-free survival during and early after the study period (gray). Transplantations are not regarded as an event, but follow-up was truncated at transplantation.

2013 because of the lack of data in patients with LVAD devices receiving a novel oral anticoagulant and the pilot design of this trial. In contrast to the RE-ALIGN trial for dabigatran in patients with mechanical heart valves, only stable patients after the first postoperative month were eligible for this trial.¹³ Therefore, potential complications caused by postoperative bleeding, early infection, or perioperative renal dysfunction did not affect this trial. Furthermore, patients with a previous stroke or a major bleeding event and patients with bleeding disorders were not included. Hence, the observed results are likely related to anticoagulation therapy and not to the underlying medical or surgical conditions of the study patients.

No differences present at randomization biased in favor of the control group. However, dabigatran patients revealed early thromboembolic events during the study period (pump thrombosis and a transient ischemic attack). The only pump thrombosis in the control group occurred in a patient with atrial fibrillation, which was previously described as a risk factor for pump thrombosis.²² A trend toward a reduced event-free survival was observed in the dabigatran group, which gained statistical significance after including the early poststudy switching period (Figure 3). The rate of pump thrombosis in the dabigatran group was increased compared with the expected rate of pump thrombosis of 0.08 per patient-year in HVAD patients.²³ Therefore, study authors voted for study discontinuation after >50% of the planned patients had been included and reached a study-defined end point. Risk factors for pump thrombosis of the HVAD system are insufficient international normalized ratio and sub-optimal anticoagulation or antiplatelet therapy.²³ Antiplatelet therapy and blood pressure were comparable between groups, indicating anticoagulation with dabigatran as main risk factor for pump thrombosis. In theory, a direct thrombin inhibitor such as dabigatran may even have advantages in the therapy of pump thrombosis because of the inhibition of free and clot-bound thrombin.²⁴ However, pump thrombosis was more prevalent in the dabigatran group. The mechanisms of thrombosis probably vary compared with patients experiencing atrial fibrillation, in whom dabigatran showed reliable results. Stasis and endothelial dysfunction in the left atrial appendage are the main contributors to thrombus formation in patients with atrial fibrillation, which represents a low-flow, low shear stress area.^{13,25} On the contrary, the contact pathway plays an important role in patients with mechanical heart valves and comparable foreign material in the blood stream. Coagulation is triggered by blood contact with artificial surfaces.²⁶ Vitamin K antagonists may be more effective by inhibiting not only thrombin (factor II) but also factors VII (activated by the tissue factor pathway) and IX (relevant in the contact pathway–induced coagulation), as well as factor X.²⁷ Furthermore, phenprocoumon has theoretically an improved safety profile compared with other vitamin K antagonists because of its limited susceptibility to CYP2C9 polymorphisms.²⁸

The present results do not support the use of dabigatran as an alternative to phenprocoumon with the applied dosing schema. The dose administered during this trial was in accordance with the recommended dose for atrial fibrillation as of 2010 and based on the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy) results.⁹ However, dabigatran later received market approval at a higher dose in the United

States compared with our trial.²⁷ Furthermore, the RE-ALIGN trial applied a higher dose compared with our investigation. RE-ALIGN was designed to obtain trough plasma levels of >50 ng dabigatran as the primary study end point. Patients received 150 mg twice daily (CRCL <70 mL/min), 220 mg twice daily (CRCL 70–109 mL/min), and 300 mg twice daily (CRCL ≥110 mL/min), which was more than double the dose compared with the dosing scheme of this trial.¹³ However, the RE-ALIGN trial showed not only excess bleeding but also increased thrombotic events despite the high dosing. We can only speculate about the effects of a higher dose in LVAD patients but doing so in regard to a possible reduction of the number of thromboembolic events may be ill-advised considering the results of the RE-ALIGN study. A nonrandomized observation applying dabigatran at doses of 110 to 150 mg BID previously reported comparable event rates for vitamin K antagonists and dabigatran during LVAD therapy.²⁹ This observation of 7 consecutive HeartMate II patients has to be interpreted with caution. All study patients were switched to dabigatran after an event (bleeding or thromboembolism) while receiving vitamin K antagonists, and those events were calculated for comparison, which may explain the differences in event rates.

Limitations

The small sample size of this study limits the ability to obtain statistically significant results. Throughout the course of this study, guidelines in regard to dabigatran dosage and monitoring changed fundamentally. Dabigatran dosages used for the duration of this trial adhered to the recommended dosage guidelines for approved indications in the year 2010, such as atrial fibrillation and deep vein thrombosis. Current state of research indicates regular drug monitoring of dabigatran to confirm the anticoagulant effects via ecarin-based assay and dilute thrombin clotting time assay, respectively.^{30,31} Standard testing and monitoring procedures had not yet been adopted by the medical community at the beginning of this trial, and attempts to collect relevant data proved unreliable. For these reasons, as well as taking into account that dabigatran was, at that time, marketed as not requiring regular monitoring, it was decided not to adjust the dose according to the laboratory measurements.

Conclusions

Thromboembolic events on dabigatran led to early termination of a randomized controlled trial of dabigatran versus phenprocoumon in LVAD patients.

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This project was funded by HeartWare, Inc with an unrestricted research grant. Study medication (dabigatran etexilate) was provided by Boehringer Ingelheim Pharma GmbH and Co KG. Funding parties had no role in study conduct or interpretation of results.

Disclosures

Dr Wolzt has received speaking fees from Boehringer. Dr Zimpfer is a consultant for HeartWare Inc. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The incidence of thromboembolic and bleeding events in the left ventricular assist device (LVAD) patient population significantly impairs clinical outcome. An optimized anticoagulation strategy represents an unmet clinical need, and prophylactic oral anticoagulation during LVAD therapy is still under intensive discussion. Theoretically, novel oral anticoagulants may offer clinical benefits. Therefore, this randomized clinical trial was initiated. Patients were randomized to receive either phenprocoumon or dabigatran in addition to aspirin for long-term anticoagulation. Treatment duration was scheduled for 1 year and stopped after observation of a primary end point. Dabigatran dose was 110 and 75 mg BID in patients with normal or impaired renal function, respectively. The study was stopped prematurely for safety reasons as thromboembolic events occurred in 4 subjects receiving dabigatran (50%) and in 1 receiving phenprocoumon (13%; $P=0.28$). The data provide preliminary evidence that dabigatran etexilate should not be used for anticoagulation in LVAD patients. This report contradicts 1 previous case series discussing a potential application of dabigatran in LVAD patients. Therefore, our study suggests that clinical trials are needed to evaluate novel oral anticoagulants in LVAD patients, and that case series may not be appropriate to influence practice.