Original Research

Dabigatran Etexilate as Second-Line Therapy in Patients with a Left Ventricular Assist Device

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Introduction: Administration of anticoagulation is mandatory in patients with left ventricular assist devices (LVADs). Vitamin K antagonists require regular monitoring and dosage adjustment. Dabigatran administered in a standard dose twice daily is more convenient and achieves a stable anticoagulant effect, but its effectiveness and safety in patients with LVADs has not been investigated. The objective of the present study was to evaluate whether dabigatran can be used safely as a second-line anticoagulation option in patients with a HeartMate II (HMII) LVAD.

Methods: The study population consisted of 7 consecutive patients with end-stage heart failure who underwent HMII implantation and sequentially received acenocoumarol and dabigatran. Occurrence of stroke, systematic embolism, device thrombosis and major or life-threatening bleeding were included in the analysis. An acute decrease in plasma hemoglobin >2 g/dL or a need for transfusion of at least 2 units of packed red blood cells (PRBC) was defined as major bleeding, while an acute decrease in plasma hemoglobin >5 g/dL, fatal, symptomatic intracranial bleed, need for transfusion of at least 4 units PRBC, or association with hypotension requiring the use of intravenous inotropic agents or surgical intervention was defined as life-threatening bleeding.

Results: The duration of follow up was 1564 ± 292 days. Patients received acenocoumarol for 855 ± 246 days, followed by dabigatran for 708 ± 368 days. The rates of thromboembolic events were similar under dabigatran and acenocoumarol treatment: strokes, 0.094 vs. 0 /patient-year, p=0.36; systemic embolism, no event in either group; and device thrombosis, 0.053 vs. 0.258 events/patient-year, p=0.19, respectively. Compared to an adjusted acenocoumarol dose, the standard dabigatran dose resulted in similar rates of life-threatening bleeding, but significantly lower rates of major bleeding (0.18 vs. 0.27 bleeds/patient-years, p=0.76, and 0.047 vs. 0.547, p<0.001, for dabigatran and acenocoumarol, respectively).

Conclusions: The safe and effective use of dabigatran as a second-line anticoagulation therapy in patients with HMII seems feasible. However, these data must be confirmed in a randomized study.

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The prophylactic administration of anticoagulation therapy is mandatory in patients with left ventricular assist devices (LVAD).[1,2] For patients supported with second-generation, continuous flow devices, bleeding appears as a more common complication than thrombosis and a more difficult one to prevent or treat.[3-5] Continuous flow devices (axial or centrifugal) have been associated with two comorbidities that promote bleeding: an acquired deficiency of functional von Willebrand factor[6-9] and increased prevalence of gastrointestinal arteriovenous malformations.[10,11] Although the exact pathophysiology of these abnormalities remains only partially explained, the role of non-pulsatile or

reduced-pulsatility flow is considered paramount for their development.

In addition to the flow pattern in these patients, coumadin anticoagulants also play an important role in the development of bleeding complications, because of the well-known difficulties in achieving and maintaining anticoagulant effects within a pre-specified range. Even in well designed clinical trials, the percentage of patients achieving the target international normalized ratio (INR) was only 55-60%.[12] Coumadin's effectiveness is closely associated with liver function, interactions with other drugs, or certain foods.[13] Frequent monitoring of the anticoagulative effect and dosing adjustments are required, but despite these measures[14] values are often below or above the target range; even extreme deviations are not infrequent.

As bleeding events constitute a major limitation of coumadin anticoagulation in LVAD patients, a safer, more practical and effective alternative therapy could maximize these patients' benefit by reducing complications and maximizing the therapeutic index.

Dabigatran etexilate, a novel direct thrombin inhibitor, has been shown to be effective for the prevention of deep vein thrombosis postoperatively and is approved for this indication. Recently, at a dose of 110 mg bid, it was shown to be non-inferior to warfarin for the prevention of thromboembolic complications in patients with non-valvular atrial fibrillation, while causing significantly fewer bleeding episodes.[15] Dabigatran was superior for the prevention of thromboembolic complications at the dose of 150 mg bid, while causing the same number of bleeding episodes in the same patients. Interestingly, in a subanalysis of the RE-LY data, dabigatran in both dosage regimens caused significantly less bleeding in patients less than 75 years old.[16]

Dabigatran has a more predictable anticoagulant effect and is less susceptible to interactions with other medications or food.[17] Monitoring and dose adjustments are not required; therefore, at least in theory, it could be a very attractive and convenient agent for anticoagulation of LVAD recipients. However, its effectiveness and safety in patients with LVADs have not been investigated so far.

The purpose of the present study was to investigate whether dabigatran could be effective in preventing stroke, non-central nervous system (CNS) systematic embolism, or device thrombosis in patients supported with HeartMate II LVADs who had suffered bleeding and/or thrombotic episodes under acenocoumarol, and at the same time to evaluate its safety, i.e. the incidence of bleeding.

Methods

Data regarding thrombotic and bleeding events were collected for retrospective analysis from seven consecutive destination therapy patients supported by a HeartMate II device who initially received optimal anticoagulation therapy with acenocoumarol and aspirin and were subsequently switched to dabigatran etexilate after experiencing at least one serious anticoagulation-related (thromboembolic or hemorrhagic) adverse event. All patients were eligible to receive dabigatran (no mechanical heart valves, glomerular filtration rate >30 mL/min, no concomitant use of potent glycoprotein P450 inhibitors). Patients who had experienced a bleeding event were administered dabigatran at a dose of 110 mg twice daily; patients who had experienced a thrombotic event under acenocoumarol were switched to a high dose of dabigatran (150 mg twice daily). All patients (both dabigatran regimens) concomitantly received aspirin in a dose of 80 mg daily. The hospital's Institutional Review Board gave its approval for the investigational use of the drug and all patients gave written informed consent for the off-label use of dabigatran.

The events that were recorded and included in the analysis were the occurrence of stroke, non-CNS systematic embolism, device thrombosis, and major or life-threatening bleeding, under the two treatment regimens. Major and life-threatening bleeding events were defined in a similar way as in the RE-LY trial, as follows:

- A decrease in the value of plasma hemoglobin of at least 2 g/dL within no more than a month from the previous measurement, or a need for transfusion of at least two units of packed red blood cells (PRBC), was defined as major bleeding.

- A decrease in plasma hemoglobin of at least 5 g/dL within no more than a month from the previous measurement, fatal, symptomatic intracranial bleed, a need for transfusion of at least four units of PRBC, or association with hypotension requiring the use of intravenous inotropic agents or surgical intervention, was defined as life-threatening bleeding.[15]

- Due to the poor sensitivity of current imaging modalities for the detection of the presence of thrombus inside the device, device thrombosis was defined on the basis of abnormal pump parameter values (pump flow, pump power, pulse index, pump speed) in the absence of any other detectable reason for these abnormalities, accompanied by significant hemolysis (lactate dehydro-

genase values >1500 IU/L or three times the previous plasma level, or an increase in free plasma hemoglobin).[1]

When device thrombosis was diagnosed, patients were immediately switched to continuous intravenous heparin infusion.

The incidence of adverse events after the implantation of an LVAD is particularly high during the initial post-implant period.[4] In order to rule out a potential time effect, events during the first one month following implantation, during which the patients were also treated with unfractionated or low-molecular-weight heparin, were excluded from the analysis. All complications were expressed as events/patient-year. Comparisons between the two groups were performed using the paired t-test. A two-sided p<0.05 was considered statistically significant.

Results

The mean duration of patients' follow up post-discharge was 1564 ± 292 days. Patients received acenocoumarol for 855 ± 246 days, followed by dabigatran

etexilate for 708 ± 368 days. The major events leading to discontinuation of coumadin therapy are listed in Table 1, while major events under dabigatran are listed in Table 2. The mean time within therapeutic range (TTR) for patients under coumadin, defined as INR measurements between 1.5 and 2.5, was 64.8%, similar to that reported in the RE-LY trial.[18]

Similar rates of thromboembolic events were observed with dabigatran and acenocoumarol treatment: strokes, 0.094 ± 0.25 vs. 0 /patient-year, p=0.36; systematic non-CNS embolisms, no event in either group; and device thromboses, 0.053 ± 0.148 vs. 0.258 ± 0.49 events/patient-year, p=0.19, respectively. The stable dabigatran dose resulted in similar rates of bleeding events (0.82 ± 0.6 vs. 0.22 ± 0.46 events/patient-year, p=0.082) and life-threatening bleedings (0.27 ± 0.59 vs. 0.18 ± 0.47 bleeds/patient-years, p=0.76), for acenocoumarol and dabigatran, respectively. Importantly, the rates of major, non life-threatening bleeding were significantly higher with acenocoumarol therapy compared to dabigatran (0.547 ± 0.11 vs. 0.047 ± 0.12 events/patient-year, p<0.001) (Figure 1).

Table 1. Incidence of thrombotic and bleeding events during treatment with acenocoumarol.

Pt	Age at implantation (years)	Sex	Heart failure etiology	Time under LVAD support (days)	Duration of acenocoumarol therapy (days)	Time within therapeutic range (% of total measurements)	Reason for change to dabigatran (INR value during the episode)
1	66	M	Ischemic	1934	1274	58	One decrease in Hgb (1.93) and one episode of gastrointestinal bleeding (2.45)
2	61	M	Non-ischemic	1067	1032	79	Two decreases in Hgb (2.14 and 2.5) and one episode of life-threatening gastrointestinal bleeding (3.2)
3	52	M	Ischemic	1557	975	55	One intramuscular bleed with compartment syndrome (3)
4	56	M	Non-ischemic	1338	755	69	One episode of gastrointestinal bleeding (2.2)
5	57	M	Ischemic	1695	682	53	One episode of gastrointestinal bleeding (2.7) and one episode of thrombosis (1.9)
6	52	M	Ischemic	1554	575	69	Two episodes of thrombosis (2.4 and 2.8) and one decrease in Hgb (2.24).
7	56	M	Ischemic	1805	698	68	Three episodes of life-threatening gastrointestinal bleeding (1.87, 1.55 and 1.72) and one decrease in Hgb (2.1)

LVAD – left ventricular assist device; Hgb - hemoglobin.

Table 2. Incidence of thrombotic and bleeding events during treatment with dabigatran.

| Pt	Age at first treatment with dabigatran (years)	Sex	Heart failure etiology	Time under LVAD support (days)	Duration of dabigatran therapy (days)	Major events under dabigatran therapy (aPTT value during the episode)
1	69	M	Ischemic	1934	660	No events
2	64	M	Non-ischemic	1067	35	No events
3	56	M	Ischemic	1557	582	No events
4	59	M	Non-ischemic	1338	583	Two life-threatening gastrointestinal bleeds (42.6 and 28.9)
5	58	M	Ischemic	1695	1013	No events
6	55	M	Ischemic	1554	979	One episode of thrombosis (73)
7	59	M	Ischemic	1805	1107	One major gastrointestinal bleed (41) and two ischemic strokes (44.5 and 40.6)

aPTT – activated prothrombin time.
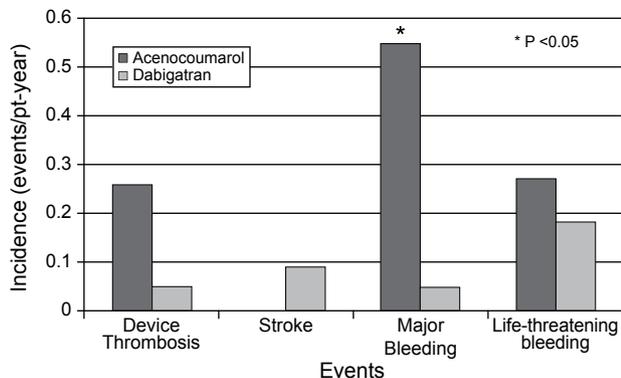
Figure 1. Comparison of event incidence under the two treatment regimens.

Discussion

The novel and significant finding of this study is that dabigatran etexilate seems to be an effective and safe second-line anticoagulation option in patients with HeartMate II LVADs who have previously experienced serious anticoagulation-related adverse events while treated with classical coumadin agents.

It is worth mentioning that our patients were switched to dabigatran after the occurrence of at least one serious adverse episode on acenocoumarol. Although the TTR was close to 65%, comparable to that achieved in the RE-LY trial, the patients experienced bleeding events. Most of the bleeding episodes occurred when the INR was actually within the desired range (Table 1). This indicates that the bleeding episodes were not due to suboptimal adjustment of the acenocoumarol dose.

Second-generation continuous-flow devices have

significantly improved prognosis in advanced heart failure, both prolonging survival and improving the patients' quality of life.[3] However, bleeding appears as the most frequent life-threatening complication for patients under continuous flow LVAD support. At the same time, LVAD patients remain at continuous risk of device thrombosis,[3] which may require emergent heart transplantation or device exchange and predisposes to life-threatening or disabling thromboembolic events. It is therefore necessary to maintain a balance between adequate anticoagulation and avoidance of excessive bleeding.

Coumadin analogues are the most widely used oral anticoagulants, representing the tenth most frequently prescribed drug in the USA.[19] Nevertheless, despite the accumulated clinical experience, their optimal use is still subject to significant difficulties, attributable both to their narrow therapeutic index and to the individual variability in the patient's response to their effect.[20]

Major bleeding, which is recognized as the most common adverse event arising from the use of coumadin, occurs in approximately 7-8% of patients annually and is associated with increased mortality.[21] Even minor bleeding events are important, despite their non-significant effect on mortality, since they lead to potentially preventable visits to the hospital, increased costs of care, reduced rates of patients' compliance with therapy and impaired quality of life.

It is well documented that, with coumadin analogues, anticoagulation levels outside the therapeutic range are more common during the period of dose adjustment.[22] Dose titration and stabilization can be challenging, because of the genetically and envi-

ronmentally determined variability of the drug's anticoagulative effect.[20] Characteristically, the weekly dose of warfarin required for the same level of INR can vary among patients from 4.5 to 77 mg.[23] Different variants of genes implicated in the metabolic cycle of warfarin are responsible for this variability in the response. In addition, sex, age, and body weight, as well as concomitant conditions such as heart failure, coronary disease, diabetes mellitus, thyroid or liver disease, can influence the anticoagulative effect produced by the same dose of coumarin. The same is true for a variety of other environmental factors (diet, medication, alcohol consumption, number and specialty of treating physicians). All these limitations in the use of coumadin mandate several modifications to patients' lifestyle and regular monitoring of anticoagulation; this inevitably leads to significant compliance issues.

LVAD patients have some characteristics that render them specifically susceptible to the drawbacks associated with coumadin therapy. These patients suffer from heart failure, which affects the response to coumadin and is also correlated with a 70% increase in the risk of bleeding.[13] These patients are on multiple drugs, and their interactions with vitamin K antagonists necessitate frequent monitoring and dose adjustments. Despite regular monitoring, many studies have shown that LVAD patients frequently have INR levels outside the desired range. This exposes them to the risks of thromboembolism or bleeding.[24] Additionally, patients supported with LVADs are at risk for development or worsening of right ventricular dysfunction, even long after the time of implantation.[25,26] Liver failure is one of the most frequent, severe, and difficult to treat consequences of right ventricular failure. Anticoagulation with vitamin K antagonists is particularly challenging in the setting of hepatic dysfunction, since patients often show dramatic responses to very low doses of coumadin, and bleeding becomes a common adverse event.[27] Last but not least, infections, necessitating oral or even parenteral administration of antibiotics, are a common complication of LVAD support. Antibiotics are among the medications that have significant interactions with the metabolism of coumadin analogues.

One the other hand, the new oral direct thrombin inhibitor, dabigatran etexilate, has several features that make it an attractive option for this subset of patients. It is administered in a standard dose twice daily, which confers stable anticoagulation, obviates the need for regular monitoring and dose adjustment,

has an effect independent of liver function, and exhibits significantly less interaction with food, drinks, and medications. Based on the findings of our study, it seems that the stable regimen of dabigatran may be an option for the subset of LVAD patients who fail to achieve a satisfactory anticoagulative effect under vitamin K antagonists. If this proves to be the case in larger prospective trials, it may constitute a major breakthrough in the chronic management of patients with the Heartmate II LVAD.

Of course, dabigatran also has disadvantages and limitations. The most obvious one is cost; dabigatran is considerably more expensive than vitamin K antagonists. However, for the indication of atrial fibrillation, this agent has been shown to be cost-effective in the subgroup of patients who are at high risk for bleeding or cannot maintain a stable INR within the therapeutic range.[28,29] Continuous flow LVAD patients form a population at particularly high risk for bleeding; it is reasonable to assume that they are good candidates for this novel treatment, if dabigatran therapy is indeed proven to reduce bleeding in this setting.

The most important limitation of dabigatran treatment, however, is the lack of a specific antidote that could rapidly and reliably reverse the anticoagulative effect, in case serious bleeding occurs or urgent surgery is required. The administration of plasma together with blood transfusions, which are proposed in life-threatening situations, are only supportive measures and not a causal treatment. The administration of concentrated coagulation factors, though effective theoretically, has not been adequately tested in clinical practice. Nevertheless, dabigatran is only sparsely bound to plasma proteins, therefore dialysis can be considered an option in critical cases. The short half life of dabigatran limits this risk to some degree; however, it is a parameter that clinicians should always weigh against potential benefits.

Dabigatran is mainly excreted by the kidneys, and renal impairment results in elevated plasma concentrations and a prolonged drug half-life.[31] Compromised renal function is a common finding in patients with end-stage heart failure who require circulatory assistance with an LVAD; therefore, only those with adequate kidney function (estimated glomerular filtration rate of at least 30 mL/min) should be considered eligible for this alternative anticoagulation regimen.

Overall, the favorable, though only indicative, results of this small study suggest that this agent ap-

pears to be an attractive option for the management of LVAD patients who have a poor result from treatment with coumadin analogs. Nevertheless, only larger, prospective, randomized trials can provide definite answers regarding the role of this novel drug in the management of LVAD recipients.

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