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STUDY DESIGN

Apixaban in bridge to transplant and destination LVAD - rationale and study design: the ApixiVAD trial

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Abstract

Aims Use of novel anticoagulation in mechanical circulatory support is controversial. We report the rationale and design of the ApixiVad pilot trial, a pilot study testing the safety of apixaban as an anticoagulant in patients bridged to transplant (BTT) or for destination (DT) with Heartmate 3 (HM3) left ventricular assist device (LVAD).

Methods and results Apixaban has been used in small non-randomized cohorts in LVAD patients and shown to be effective in *ex vivo* studies. The ApixiVAD study examines apixaban use in a multicentre, international, open-label, randomized, controlled trial aiming to include 50 BTT or DT HM3 patients with a 1:1 randomization ratio. This event-driven study has a maximum follow-up period of 24 months with interim analysis at 6 months. The primary outcome is death, thromboembolic events and major bleeding, including operative bleeding and immediate transplant outcomes. The secondary outcome focuses on patients' quality of life related to anticoagulation. This investigator-driven pilot study is not powered to determine the non-inferiority of apixaban. An increase in primary outcome in the apixaban group of 20% will be considered a signal of harm.

Conclusions A positive outcome in the ApixiVAD study would provide the basis for future, larger, pivotal anticoagulation trials in LVAD patients.

Keywords LVAD; apixaban; DOAC; HeartMate 3

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Bruno Schnegg and Ricardo Deveza have equal contribution.

Introduction

Standard of care

Left ventricular assist devices (LVADs) have been demonstrated to improve outcomes in patients with advanced heart failure refractory to optimal medical therapy, both as a bridge to transplant (BTT) strategy and as destination therapy (DT).[1,2]

When blood comes into contact with foreign inorganic materials, particularly metals, the human coagulation cascade is activated.[3] Continued activation of the coagulation system in the presence of LVAD, through which all or almost all of the cardiac output flows, requires therapeutic anticoagulation to prevent pump thrombosis. The current standard of care in VAD anticoagulation is using vitamin K antagonists (VKAs), such as Warfarin or Marcoumar.[4]

VKAs provide systemic anticoagulation by inhibiting the vitamin K-dependent synthesis of coagulation factors II, VII, IX, and X, as well as proteins C and S, resulting in a downstream reduction in the activated factor II-dependent conversion of fibrinogen to fibrin and subsequent thrombus formation.[5] The international normalized ratio (INR) is used to titrate the degree of anticoagulation. INR provides a snapshot assessment of coagulation status, with considerable unmonitored time during which INR may be above or below the therapeutic window. Unfortunately, many drugs and dietary substances can alter the effect of VKAs, either by competitive antagonism, modification of cytochrome P-450, or enhancement of anticoagulant effects. Current data suggests that the time in therapeutic range (TTR) in a population of patients with an LVAD is low, around 45%,[6] and that the TTR is inversely and significantly proportional to the percentage of haemocompatibility-related complications.[7]

Haemocompatibility-related complications are the two most significant threats to morbidity and mortality in the VAD population, with 3 to 5 events/100 patients/month.[8]

Direct oral anticoagulants in mechanical devices

The advent of direct oral anticoagulants (DOACs), which inhibit the action of specific coagulation factors such as FXa (rivaroxaban, edoxaban, and apixaban) or FIIa/thrombin (dabigatran), have overtaken VKA's as preferred anticoagulation for the prevention of venous thromboembolic events and stroke in atrial fibrillation.[9]

The first trial to use of DOACs, namely, dabigatran, in patients with mechanical heart valves RE-ALIGN trial[10] was halted prematurely due to excessive haemocompatibility related complications in the dabigatran group. A contemporaneous trial in patients with VADs was also terminated prematurely for the same reason.[11] This has resulted in the contraindication of the use, not only of dabigatran but also of the entire class of DOACs in patients with mechanical valves and LVADs over the last 10 years.[12]

Evidence of the use of apixaban in left ventricular assist device patients

Before embarking on a new clinical trial using a DOAC, an *ex vivo* study was needed comparing VKA's, FXa inhibitors and FIIa inhibitors. An *in vitro* trial on time to thrombus formation in a mock-loop using human blood with warfarin, low and high dose apixaban (2.5 and 5 mg BID, respectively) and dabigatran showed low dose of apixaban (2.5 mg BID) to be comparable to therapeutic anticoagulation with warfarin (INR of 2.8) and superior to dabigatran.[13] Despite the absence of prospective controlled trials, DOACs have been used (off-label) in patients with LVAD and described in multiple case reports and case series. A systematic review of 74 patients switching from VKAs to DOACs concluded, with all the biases inherent in this type of review, that DOACs appeared to be a possible alternative to VKAs.[14] In 2022, a non-randomized study with balanced groups retrospectively compared patients on VKAs versus switched to apixaban. This study found identical thromboembolic events in both groups but less bleeding in the apixaban group.[15] VKA remains the only approved form of oral anticoagulation in the most recent JHLT MCS Guideline Update[16] and HFSA Guidelines,[17] unchanged over the last decade, despite advances in devices.

Study design

In view of the *in vitro* study and the numerous case series, we designed the ApixiVAD study, an international (Australia and Switzerland), randomized, controlled, non-inferior pilot trial designed to test the safety of apixaban 2.5 mg BID against standard of care in patients with LVAD-HeartMade 3 (HM3) both in patients implanted as destination therapy (DT) and in patients listed for cardiac transplantation (BTT).

Our hypothesis is that apixaban in patients with LVAD is equivalent to standard antivitamin K therapy in terms of haemocompatibility (H0). The alternative hypothesis (H1) is that there is an inferiority of apixaban in patients with LVAD with a 20% or more increase in the proportion of thrombotic events bleeding and death.

Patients are randomized in a 1:1 ratio between standard medical management (VKa's) and treatment with apixaban 2.5 mg BID. No other changes to the treatment (including the antiplatelet medication) will be made. The study is event-driven, with a sample size of 50 patients. The first patient was randomized in January 2022, and the recruitment is expected to end in late 2024. The mean duration of follow-up will depend on the proportion of DT patients, the waiting time for BTT patients and the event rate. Maximum follow-up will be 24 months.

Objectives

The aim of this pilot study is to investigate, in a controlled environment, the haemocompatibility of reduced-dose apixaban in patients implanted with an LVAD. The study is not powered to show superiority, nor non-inferiority. The absence of a danger signal, that is, the absence of a significant increase in haemocompatibility events (thrombotic events, and bleeding and death) in patients on apixaban, will validate the study design and enable a larger, national, non-inferiority trial of reduced-dose apixaban in patients with LVADs.

Outcomes and endpoints

Our primary combined outcome is a composite of thromboembolic events, bleeding and death. From randomization to transplantation, or a maximum of 2 years follow-up (*Table 1*). Primary outcome events are assessed in two stages. The events are reported to a steering committee composed of the investigators from the different sites and then transmitted to a Data Monitoring and Safety Board.

The secondary outcomes include the factors influencing haemocompatibility events, the satisfaction of patients regarding anticoagulation as well the safety of apixaban (lack of excess bleeding) in the peri-transplant period in BTT patients.

The patients included in our study will be both DT patients and patients listed for cardiac transplantation. This means

Table 1 Primary and secondary outcomes

Primary outcomes	Selected[c] secondary outcomes
The primary outcome is a component of • Death • Suspected or confirmed pump thrombosis[a] • Ischaemic or haemorrhagic stroke • Other thrombo-embolic events, excluding stroke and pump thrombosis • Major bleeding[b]	• Major haemolysis[a] • Baseline (1 and 3 months after randomization) haemostasis testing using a thrombin—anti-thrombin (TAT) assay • Time in therapeutic range (TTR) in the warfarin group • Quality of life assessment using the ACTS-scale (patient satisfaction score) • Influence of digoxin, ACE inhibitors, and PPIs on the incidence of bleeding • 30-day survival post-transplantation • Need for transfusion and quantity of blood products used during transplantation • ICU length of stay following heart transplantation

[a]As per the definition from INTERMAC 2016.[32]
[b]Define as transfusion of four or more units of packed red blood cells in 24 h and/or hospitalization.
[c]The secondary outcomes not described here are the individual components of the primary outcome and their timing of occurrence

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Patients implanted with a HeartMate3 (HM3, Abbott) ventricular assist device in the left ventricle • Body weight equal to or greater than 60 kg • Patients aged 18 years and older • Creatinine clearance greater than 25 mL/min and creatinine level <221 mcmol/L • TTR in the preceding 4 weeks of 60% or more • Implementation of the LVAD dating from at least 2 months • Participants able to give an informed consent	• Stroke within 14 days or severe, disabling stroke within 3 months of recruitment • History of conditions associated with increased bleeding risk (major surgery within the previous month; history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding; gastrointestinal haemorrhage within 6 months prior to recruitment; chronic haemorrhagic disorder; known intracranial neoplasm, arteriovenous malformation, or aneurysm; requirement for treatment with aspirin at a dose greater than 100 mg per day; simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel, prasugrel, and ticagrelor)) • Alanine transaminase >5× ULN or known cirrhotic liver disease • Active alcohol or illicit drug use or psychosocial reasons that make study participation impractical • Patients with known human immunodeficiency virus (HIV) infection • Patients taking medications or other substances known to be potent inhibitors or inducers of the CYP3A4 enzyme • Women who are pregnant or breastfeeding • Allergy to apixaban • Allergy to any of the component ingredients of andexanet-alpha

that the endpoint will not be identical for all patients. The endpoints are as follows: the occurrence of one of the components of the primary outcome, reaching 24 months of follow-up or heart transplantation.

Inclusions and exclusion criteria

Inclusion criteria include patients implanted with an isolated HM3 LVAD at one of the study sites. Implantation must have taken place at least 2 months before inclusion, and the patient must not meet the criteria for a dose reduction of apixaban (weight <60 kg, renal impairment with eGFR <25 mL/min/m^2). For the control group to be of good quality, the TTR at randomization must be at least 60% for the lat months prior to randomization (*Table 2*). The exclusion criteria are designed to exclude patients at high risk of bleeding or thrombosis (mainly patients with a history of strokes or relevant bleeding) and patients taking drugs that interact with apixaban and increase or decrease its blood levels (*Table 2*).

Patient randomization

Randomization is 1:1 with stratification by gender and levels of renal impairment (eGFR greater than or <60 mL/min/m^2). To reduce the predictability of allocation in the context of an open trial, blocks of 2, 4, and 6 patients, determined randomly, will be used for allocation.

Intervention

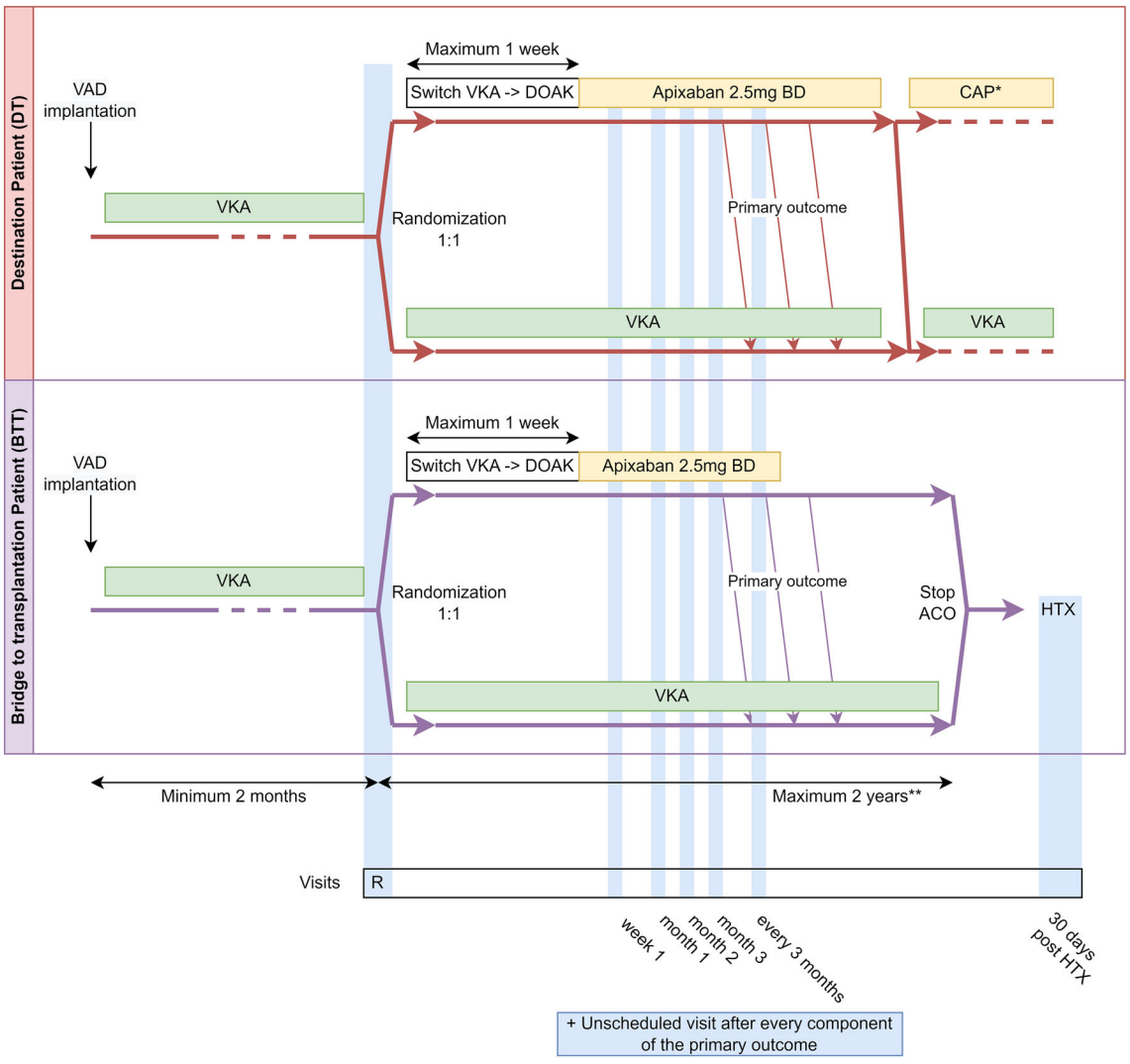
Patients randomized to the apixaban group immediately stopped their VKA's. If their INR is below 2.0, they can begin treatment with apixaban on the evening of randomization. If not, they are asked to perform one INR daily until they reach a value below 2.0. The study team contacts them every day to

discuss starting treatment. The rest of the medication remains unchanged.

The follow-up plan is shown in *Figure 1*. At these follow-up appointments, all patients are given information on the best practices to adopt when wearing an LVAD, including promotion of smoking cessation, reinforcement of avoidance of alcohol excess and illicit drug use, systematic use of endocarditis prophylaxis during dental treatment, and promotion of the use of proton pump inhibitors (PPIs). Upon the occurrence of any of the primary Outcome components, patients are switched back from apixaban to VKA's. In DT patients reaching 2 years of follow-up, the possibility of remaining on apixaban treatment will be offered to patients following the approval of a request for reimbursement by the health insurance.

The BTT patients included in the study are integrated without any modification in transplant eligibility by allocation system. Donation after brain or circulatory death are both possible. In the event of heart transplantation, patients randomized to apixaban are asked to withhold any further apixaban until operation time. As andexanet-alpha is not available in Australia, BTT patients undergoing transplantation are managed with prothrombin-complex concentrate, and a cytokine filter used in-line with cardiopulmonary bypass to adsorb residual apixaban during surgery.[18,19] Transfusion requirements (platelet, prothrombin complex concen-

Figure 1 Study schedule. *CAP if desired by the patient and authorized by the health insurance. **If no transplantation during the 2 years of follow-up, patients in the apixaban group can have access to CAP if desired and authorized by the health insurance. BD, twice daily; CAP, continuous access protocol; DOAC, direct oral anticoagulant; VAD, ventricular assist device; VKA, vitamin K antagonist.



trate, packed red blood cells, and clotting factors) will be recorded for all patients. Intensive care length of stay and hospital length of stay will be recorded for all patients out to 30 days post transplantation.

Statistic comparison

The ApixiVAD study is a pilot study. Given our estimated event rate of 20% for the primary outcome (based on the results of the Momentum3 study[20]), if there is truly no difference between the standard and experimental treatment, then 138 patients are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group of more than 20%.

As mentioned before, the aim of this pilot study is to investigate, in a controlled environment, the safety of reduced-dose apixaban in patients implanted with a LVAD. In this context, we defined the margin to detect a signal of harm as an increase in the primary outcome event rate of 20% or higher in the apixaban group as compared to the warfarin group.

Descriptive statistical methods will be applied to describe the study population in terms of risk factors, operative characteristics and outcomes; continuous variables will be presented as mean and standard deviation and compared with the independent samples *t*-test between study groups; total numbers and proportions will be reported for categorical outcomes and compared with Fisher's exact test. The Kaplan–Meier method with a log-rank test will be used to compare event-free survival and the components of the composite primary outcome (death, thromboembolic or haemorrhagic events). The life table method with a Wilcoxon–Gehan test will be used to calculate the median time to the end of the study.

Ethics and follow-up

The Steering Committee is responsible for the clinical and scientific conduct of the study and the publication of results. An independent Data and Safety Monitoring Board reviews interim analyses (every 3 months) and all adverse events. The study has been approved by the relevant Research Ethics Committee (in Australia: 2020/ETH00695 in Switzerland: 2023-00632) and registered in Australian New Zealand Clinical Trials Registry (ACTRN12621000956808). The trial is conducted according to the Australian and Swiss legislation, Good Clinical Practice and the 2002 Declaration of Helsinki.

Discussion

The issue of anticoagulation in patients with LVAD is one that, despite the technological advances of recent years, remains frustrating. Despite a significant reduction in thrombosis with HM3, there remain significant haemorrhagic complications. While cardiology and neurology have largely moved beyond VKA to the safer and more effective DOAC, these agents remain contra-indicated in MCS management.

Why dabigatran failed in mechanical devices

There are a number of reasons for the failure of dabigatran in MCS patients. While inhibition of a single FIIa molecule by a dabigatran molecule will stop the downstream coagulation cascade, a more potent upstream process may overwhelm dabigatran's ability to inhibit FIIa, given that a single FXa molecule can activate more than 1000 downstream FII molecules.[21] In Andreas' study, dabigatran was introduced early in the protocol, <2 months after surgery. Cardiac surgery is associated with an inflammatory response and the release of cell-derived microparticles, which strongly promote thrombus formation. FIIa inhibition "alone" is probably insufficient in the immediate postoperative period. It should also be noted that the half-life of dabigatran is short compared with VKA's and, in patients with normal creatinine clearance, could be as short as 8 h.[22] Conventional twice-daily dosing of dabigatran may be sufficient for primary prevention (atrial fibrillation and venous thrombosis) but insufficient for the constant activation of coagulation by a metal surface. A final key consideration is the device used. In the dabigatran-LVAD trial carried the older generation pump, Medtronic HeartWare, which was known to be prone to thrombosis and has since been withdrawn from the market.

It should be noted, that since this trial was designed preliminary findings have resulted in the cessation of the PROACT-Xa trial, a randomized trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with a mechanical On-X aortic heart valve.[23] The trial was abandoned after 863 patients were randomized because the incidence of thromboembolism was 4.2% per patient-year in the apixaban group and 1.3% per patient-year in the warfarin group.[24] Full results have not been published as yet. Significant differences exist between aortic valve and LVAD devices in terms of thrombotic risk. The primary difference is that aortic valves are subject to low-zero flow across the device during diastole, whereas HM3 maintains continuous flow (with intermittent asynchronous pump speed modulation) throughout the cardiac cycle. In light of this the DSMB and central Ethics Committee was notified of the PROACT-Xa outcome, and it was agreed to continue the current ApixiVAD trial.

Dose of apixaban

We decided to use a single, reduced dose of 2.5 mg BID of apixaban in all our patients. The risk of thrombosis in patients with HM3 is low, but the bleeding rate remains elevated due to the requirement for combination full anticoagulation and antiplatelet therapy. The MAGENTUM study[25] demonstrated that sub-therapeutic anticoagulation with a VKA (INR target of 1.5 to 1.8) did not increase thrombotic or thromboembolic events. Until publication of the ARIES trial[4] our patients were treated concurrently with aspirin (as per HM3 instructions for use). Subsequently, aspirin was withdrawn in stable patients and continued on the trial. For patients on the transplant list, using a lower dose of anticoagulation reduces the risk of peri-operative complications. In the *in vitro* study comparing a range of anticoagulation, the closest anticoagulant effect to donor blood with an INR of 2.8 was apixaban 2.5 mg. A further consideration is the known shear stress on platelets and acquired von-Willebrand deficiency, while seen to a diminished extent in HM3 patients,[26] may contribute to the reduction of thrombotic risk and excess bleeding.

In this context, the overall risk of haemocompatibility complications (bleeding and thrombosis) has led us to reduce anticoagulation in order to reduce the overall risk of complications for the patient.

Why a pilot trial

Cohort data on the use of DOACs and case series in LVAD patients already exist. Carrying out a study of this type would provide little or no additional data on the subject. We decided to carry out a pilot study focusing on the safety of apixaban 2.52 mg 2×/day in patients with LVAD. A non-inferiority study would require around 400 patients per group, a number beyond the reach of an investigator-driven study.

Inclusions of bridge to transplant patients

As previously demonstrated by our team, the risk of peri-transplant bleeding in LVAD patients treated with VKA's is mainly related to doing a re-sternotomy and not to the anticoagulation itself.[27] Despite clear benefit for apixaban over VKA for atrial fibrillation patients, there remains reluctance to recommend NOACs in waitlisted heart transplant patients. One concern is that exposure to apixaban instead of VKA's could cause increased bleeding during the emergent transplant operation. However, using a lower dose of apixaban with a shorter half-life and using a cytokine filter[18] appear to be sufficient safety measures to allow the inclusion of BTT patients in the study.

Table 3 Comparison of three publicly available studies using apixaban in a randomized controlled trial in LVAD patients

		ApixiVAD	DOT-HM3	DOAC LVAD
Inclusion/exclusion criteria	LVAD type	HeartMate 3	HeartMate 3	HeartMate 3
	Delay since implementation	2 months	3 months	Not specified
	Weight	>60 kg	>60 kg	Not specified
	Age	>18 years old	18–80 years old	>18 years old
	DT/BTT	DT and BTT	Not specified	Only DT
	Kidney function	Creat. <221 mcmol/L CeaCl >25 mL/min	Creat. <221 mcmol/L CeaCl >25 mL/min	Not end-stage renal failure
	Liver function	ALT <5× ULN No cirrhosis	Bili. <43 μmol/L No cirrhosis	Bili. <43 μmol/L No cirrhosis
	Mechanical prosthetic valve	No precision	Exclusion criteria	Exclusion criteria
	Therapy with aspirin	Not mandatory	Not mandatory	Not mandatory
	Antiplatelet therapy other than aspirin	Exclusion criteria	Exclusion if need for antiplatelet therapy for reasons other than LVAD therapy	Exclusion criteria
Study design	Dose of apixaban	2.5 mg BID	Not specified	5 mg BID
	Maximum duration	24 months	12 months[b]	8 months
	Primary outcome	Survival free of any major haemocompatibility-related adverse event	Adverse events defined by INTERMACS definitions[c]	Survival free of any major haemocompatibility-related adverse event

[a]Patients with a mechanical valve have a contraindication to LVAD implantation. In this context, neither in Switzerland nor in Australia, a patient is implanted with an LVAD if they have a mechanical valve.
[b]Through study completion, an average of 1 year.
[c]Stroke (ischaemic/haemorrhagic), pump thrombosis, major bleeding, GI bleeding, peripheral arterial thromboembolic events, transient ischaemic attack, haemolysis, venous thromboembolism, myocardial infarction, right heart failure, cardiac arrhythmias, liver and kidney dysfunction, death due to any cause

The use of andexanet-alpha, a recombinant modified version of human-activated factor X, which can be used as an antidote to apixaban, was not considered for routine use in our protocol (although its use is left to the discretion of the investigators). This drug has been described as able to induce a non-reversible hypercoagulable state,[28] which may be problematic in transplant patients undergoing cardiopulmonary bypass. We have reported very preliminary results showing, in a small series, no increase in the risk of bleeding or in the duration of time spent in intensive care in patients treated with apixaban 2.5 mg before transplantation.[29]

To our knowledge, at least two other teams in the world have publicly described (ClinicalTrials.gov) relatively similar protocols, the DOT-HM3[30] study (Prague, Czechia) and the LVAD-DOAC[31] study (Virginia, USA), but the ApixiVad study is unique in several design decisions. The two key features are using a 2.5 mg dose of apixaban and including both DT and BTT patients (*Table 3*).

Glance into the future

With at least three studies currently underway testing apixaban in the setting of patients with HM3 LVAD, the beginnings of evidence could be generated. Given the very similar design, a combination of these results will be possible and may reinforce the conclusions of the individual studies. None of these studies will be of sufficient size to warrant a change in apixaban indication or MCS management until an appropriately powered pivotal outcome study is applied to apixaban against standard of therapy, VKA. The ARIES[31] study on the role of aspirin in patients implanted with HM3 (628 patients) has been completed and confirms the non-inferiority of not giving Aspirin to patients implanted with HM3. These results should be incorporated into a future randomized controlled trial using.

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Conflict of interest

BS and RC report no conflict of interest. CH has received research support, speaker's bureau, and consultancy from Medtronic, Abbott.

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