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What is the optimal anticoagulation in patients with a left ventricular assist device?

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Abstract

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was whether there is an optimal antithrombotic management for patients supported with axial-flow left ventricular assist devices (LVADs). Altogether, more than 758 papers were found using the reported search, of which 17 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. These included seven prospective and three retrospective cohort studies with a total of 538 patients with axial-flow left ventricular assist device (LVAD) (HeartMate II, Jarvik 2000, INCOR, Thoratec assist device) implanted across the world as destination therapy or bridge to transplantation. We conclude that there is a substantial alteration of the prothrombotic profile in patients with axial-flow LVADs. These abnormalities appeared to be reversible with the removal of the device and are likely to be responsible for the high incidence of non-surgical bleeding episodes reported. Warfarin seems to offer a lower thromboembolic risk compared with unfractioned heparin or low molecular weight heparin. There are reports that suggest that managing axial-flow LVAD without anticoagulation, after major bleeding complications, is possible but in all probability, these papers are subject to publication bias as poor outcomes are unlikely to have been reported. All patients with axial-flow LVAD, showed severely impaired platelet function at point of care tests. The use of warfarin (INR target 2.5), in association with aspirin at 100 mg/day, or with point-of-care tests titrated antiplatelet therapy to inhibit 70%, seems to have the best bleeding-thrombosis, and in many cases a very small dose of aspirin of 25 mg twice a day and a dose of clopidogrel of 35 mg/day, were sufficient to achieve a reduction of the maximum aggregation to less than 30%. Finally, we would like to emphasize that such recommendations are addressed only to patients with axial-flow LVAD.

Keywords: Left ventricular assist device • Oral anticoagulation • Antiplatelet agents • Antithrombotic therapy

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1]

THREE-PART QUESTION

In [patients with axial-flow left ventricular assist device] what is [the best anticoagulation strategy] to [optimize mortality and morbidity]?

CLINICAL SCENARIO

You are at a ventricular assist device (VAD) conference and the speaker is talking about the problems that they have been having with non-surgical bleeding at their institution. You are surprised as in your institution you have not had many bleeding complications, but have had a few serious ventricular assist device (VAD) thromboses, which all required thrombolysis to resolve. You wonder what the current anticoagulation strategies are around the world and resolve to check the literature.

SEARCH STRATEGY

Medline 1950 to March 2012 using OVID interface (left ventricular assist device/or LVAD.mp.) and (antithrombotic therapy/or anticoagulation.mp.)

SEARCH OUTCOME

758 papers were found using the reported search. From these, 17 papers were identified. That provided the best evidence to answer the question. They are presented in Table 1.

RESULTS

Uriel *et al*. [2], in a retrospective analysis of 79 patients with axial-flow LVAD, anticoagulated with a combination of warfarin,

Table 1: Best evidence papers

Author, date, journal, country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Uriel *et al*., 2010, J Am Coll Cardiol, USA [2] Retrospective cohort study (level 2b)	Seventy-nine HM II were reviewed for coagulation abnormalities and bleeding events + transfusion at heart transplantation, compared with that in 69 HeartMate XVE patients	Anticoagulation protocol	Warfarin in 68.3%, aspirin in 55.7% and dipyridamole in 58.2% of the patients	High molecular weight von Willebrand factor multimers were reduced in all HM II patients; 18 of these 31 (58%) patients had bleeding
		Bleeding and thromboembolic events during support	44.3% had bleeding episodes with 50% experiencing an event within 2 months of implantation. Five patients had thromboembolic events: 2 CVAs, 1 popliteal artery embolism and 2 embolic events after treatment with IV IgGn	Average INR at time of bleeding was 1.67 ± 0.53 with only 2 patients with INR > 2.5. GI bleeding was the most frequent event
Stern *et al*., 2010, J Card Surg, USA [3] Retrospective cohort study (level 2b)	Thirty-three patients undergoing long-term LVAD implantation 20 with HM II and 13 patients with other devices (non-axial continuous-flow devices)	Anticoagulation protocol	heparin (intravenous or subcutaneous) from POD 3–5 followed by transition to Coumadin therapy to a target INR of 2.0–3.0 antiplatelet therapy consisted of low-dose aspirin and dipyridamole	The authors lowered the INR target to 1.5–2.0 because of a high incidence of bleeding events
		Bleeding events during device support	Eight (40%) HM II recipients suffered at least one episode of GI bleeding while no GI bleeding occurred in recipients of other devices ($P = 0.012$)	In 3 patients with HM II and GI bleeding, warfarin was withheld for at least four months without any thromboembolic events
Demirozu *et al*., 2011, J Heart Lung Transplant, USA [4] Case series (level 4)	One hundred seventy-two patients who received HM II support	Anticoagulation protocol	Warfarin (INR 2.0–3.0), aspirin and dipyridamole	All GI bleeding episodes were successfully managed medically
		Bleeding events during device support	Thirty-two patients (19%) had GI bleeding after 63 ± 62 (range 8–241) days of support. Ten patients had GI bleeding from an AVM	
Geisen *et al*., 2008, Eur J Cardiothorac Surg, Germany [5] Prospective cohort study (level 2a)	Analysed patients with two VAD types (7 HM II; 5 Thoratec biventricular assist device) and compared them with 8 patients after heart transplantation (HTX)	Anticoagulation protocol	Anticoagulation for both systems was started with heparin (target PTT of 60–80 s) and changed to warfarin with a target INR of 3.0–3.5 for the Thoratec BiVAD and 2.5–3.0 for the HM II after removal of the chest drains. Platelet anti-aggregation was attained with aspirin 100 mg/day	Small cohort. Did not comment if the abnormal coagulation pattern recorded in the VAD group translated into higher incidence of bleeding events. Transplant group received only aspirin 100 mg/day
		Outcome	Large multimers were missing in all VAD patients. Collagen binding capacity and ristocetin cofactor activity were lower in VAD compared to HTX recipients	5/6 HTX recipients displayed normal multimer pattern

Continued

Table 1: Continued

Author, date, journal, country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Crow *et al.*, 2010, Ann Thorac Surg, USA [6] Prospective cohort study (level 2a)	Blood samples were collected before and after CF-LVAD implantation from 37 patients. Blood samples were analysed for vWF, platelet and collagen-binding ability	Hemostatic profile	All 37 patients exhibited significant loss of HMW vWF multimers within 30 days of CF-LVAD implantation	The presence of high-molecular-weight (HMW) vWF multimers were detected through gel electrophoresis. All CF-LVAD recipients had AvWS after LVAD placement
		Anticoagulation protocol	Warfarin (INR target 1.5–2.0) and aspirin	INR levels between bleeders and non-bleeders were similar
		Bleeding complications	Ten of the 37 patients experienced bleeding complications after CF-LVAD placement	The loss of HMW vWF multimers alone cannot predict bleeding risk
Meyer *et al.*, 2010, Circ Heart Fail, Germany [7] Prospective cohort study (level 2a)	Twenty-six patients received axial flow LVAD (HM II) for a median support time of 4.5 months	Hemostatic profile	In all patients on devices, severe impairment of platelet aggregation as well as a loss of large vWF multimers were found	A diagnosis of von Willebrand syndrome type 2 was established in all patients after LVAD implantation. Reversibility of this condition was found after removal of the device
		Anticoagulation protocol	IV heparin within 24 h from implantation if chest tubes drainage < 50 ml/h. Transition to warfarin after drain removal (INR target 2.5 ± 0.5) + aspirin 100 mg/day from POD 3	Platelet-related hemostasis was tested with a PFA-100 with an aspirin-independent test. If patient had AvWS aspirin was stopped
		Bleeding episodes	Incidence of 0.17 per patient-year: 8 bleeding episodes were recorded within 48 patient-years	The total follow-up period was 48 patient-years
		Thromboembolic events	No haemorrhagic or ischaemic CVAs. One fatal mesenteric ischaemia, two pump thrombosis (one after discontinuation of warfarin)	One pump thrombosis was successfully treated with lepirudin
		Mortality	One died due to mesenteric ischaemia 4 months after implantation; 1 died due to sepsis after 40 months	
Jennings *et al.*, 2011, J Thorac Cardiovasc Surg, USA [8] Prospective cohort study (level 2a)	Sixteen patients (average age: 53 years; 62% Afro-American; 81% male; 31% bridge-to-transplant). Followed up to 1-year post-LVAD implantation (HeartMate II)	Time to within the therapeutic international normalized ratio (INR) range (2.0–3.0)	Average: 51% (range 22–88%). Significantly worse than the control group: the overall clinic population (68%). The VAD population was 17% above and 32% below the therapeutic range	Small study. Suggests that HM II patients may spend less time in their target INR range than the overall anticoagulation clinic population
		Bleeding and thromboembolic events	No outpatient bleeding episodes. One patient had a transient ischaemic attack (INR 1.6)	

Continued

Table 1: Continued

Author, date, journal, country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Slaughter *et al.*, 2011, Int J Artif Organs, USA [9] Prospective cohort study (level 2a)	Thirty-four HF patients supported by a HM II axial flow LVAD implanted for destination therapy (DT). 31 M, 3 F, supported by LVAD for 30–723 days average 268 days	Anticoagulation protocol	Coumadin (0–8 mg daily dose) and aspirin (0–325 mg daily dose)	Despite high shear stresses associated with a high-speed axial flow pump, the HM II had no discernable effect on platelet activation, independently of length of support, antiplatelet and anticoagulation regimens
		Platelet adhesion markers	The soluble P-selectin marker was within normal platelet activity limits for all end points	
John *et al.*, 2008, J Thorac Cardiovasc Surg, USA [10] Case series (level 4)	Forty-five patients (mean age 57.24 ± 14.2 years) underwent implantation of the HeartMate II; 30 bridge-to-transplantation therapy, 7 DT, and 8 device exchange for a failed XVE left ventricular assist device	Anticoagulation	IV heparin 12–24 h after HM II implantation or at the point that thoracostomy tube drainage is less than 50 ml/h; Warfarin (from POD 3–5) with INR target 2.0–3.0 for the first 14 patients and 1.5–2.0 for the others; aspirin from POD 2–3 at 81 mg/day	Single-center analysis. However, as a result of significant GI bleeding among the first 14 patients, they stopped using postoperative heparin and lowered the INR to 1.5–2.0
		Average monthly INR range	Forty-one had a mean INR of less than 2.0; of those 41 patients, 21 had a mean INR of less than 1.6	
		Incidences of bleeding	Of the first 14 patients, 4 had GI bleeding and 1 pericardial tamponade (5/14; 35.7%). Of the remaining 31 patients who received only warfarin, 4 had GI bleeding, (4/31; 12.9%)	Because of recurrent GI bleeding episodes, 4 patients discontinued warfarin for about 4 months without any thromboembolic events
		Device thrombus	One suspected pump thrombus (INR, 1.3 at the time of presentation)	No thrombolytic therapy was used
Attisani *et al.*, 2010, J Artif Organs, Italy [11] Case series (level 4)	Twelve patients (10 males, 35–60 years old) with acute or end stage heart failure received the INCOR LVAD system as a bridge-to-transplantation. Mean follow-up was 10 months (cumulative 4.9 years)	Anticoagulation protocol	Heparin and warfarin: IV heparin was used until POD 4 (PTT 60–80 s). IV heparin was stopped when INR was over 2.2 The INR target was 2.8–3.2. Double antiplatelet therapy with aspirin and clopidogrel was started between the second and the fifth POD	Small cohort. Stimulators of platelet aggregation used in the test were arachidonic acid (AA), ADP, epinephrine and collagen. There were no cases of aspirin or clopidogrel resistance
		Conditions to introduce antiplatelet therapy	Platelet count over 100 000/ml. The target was to obtain a reduction of the maximum aggregation (MA)/20% with AA,/50% with epinephrine and /30% with ADP. Collagen acted as a control and should not be suppressed (MA over 50%)	In 9 cases (82%), the effective dose of aspirin was 25 mg twice a day, and in 2 (18%) it was 50 mg twice a day. In 10 cases (90%), the effective dose of clopidogrel was 35 mg/day, and in only one case, 75 mg/day
		Major and minor bleeding	Three (25%) cases of early postoperative mediastinal bleeding	No episodes of major bleeding occurred during the follow-up period

Continued

Table 1: Continued

Author, date, journal, country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
		Major and minor thromboembolic events	The rate of major and minor events was 0.09 and 0.2 per patient-year respectively	
Meuris *et al.*, 2007, Artif Organs, Belgium [12] Case series (level 4)	Ten patients with end-stage HF treated with INCOR LVAD as bridge-to-transplantation and kept on a long-term regime of low molecular weight heparin (LMWH) and antiplatelet therapy	Anticoagulation protocol	No anticoagulation during the first 12 h postoperatively. Thereafter, IV heparin (PTT60–80 s). As soon as the chest drains were removed and total platelet count was above 100 000/ml: aspirin at 80 mg two times daily; clopidogrel at 75 mg daily; and dipyridamole 75 mg three times daily. As soon as the patients were moved to the regular ward, the intravenous heparin was replaced by subcutaneous LMWHs at a therapeutic level of 1 mg/kg, twice daily	Effectiveness of the low molecular weight regime was monitored through measurement of antifactor Xa activity (base and peak levels). Antiplatelet therapy was monitored through weekly platelet function tests. No oral anticoagulation was given at any time
		Bleeding events	One patient had a fatal late intestinal bleeding	
		Thromboembolic events	Five minor TIA. Four Thrombus-related pump dysfunction. One severe stroke with concomitant intracranial bleeding fatal to the patient	
Copeland *et al.*, 2011, Artif Organs, USA [13] Case series (level 4)	Twenty-eight children, ages 1 month to 16 years. Eighteen LVAD, 7 BIVAD and 3 total artificial hearts, implanted for 3–107 days (mean 27)	Anticoagulation protocol	Heparin IV was started once chest tube drainage was <0.5 ml/kg/h . Dipyridamole was started immediately postoperatively IV at 0.1 mg/kg/h in children <6 years old, 50 mg (age 6–10 years) or 100 mg (>10 years) every 6 h. Aspirin was started at 2–10 mg/kg/min after plt > 150 000 mm^3. Dosage was increased in larger children by 162–325 mg for each 100 000 plt above 150 000. Pentoxifylline 400 mg × 3/daily was used in >6-years old	VAD anticoagulation is more difficult in children. 20/28 (71%) were discharged from the hospital. Antiplatelet effect assessed with thromboelastography (TEG), platelet aggregation studies
		Deaths	Eight deaths (29%): 4 embolic, 1 graft failure, 2 anoxic brain damage and 1 postexplant heart failure	
		Thromboembolic and bleeding complication	Six reoperations for bleeding (21%); 7 strokes (25%) and 3 visceral emboli (11%)	
Saito *et al.*, 2001, Eur J Cardiothorac Surg, UK [14]	Animal study. The Terumo continuous flow left ventricular assist system (T-ILVAS; a centrifugal pump with a	Anticoagulation & outcome All animals appeared completely normal for up to 210 days. At speeds between	No anticoagulation was given after implantation	All animals were electively euthanized between 3 and 7 months postoperatively. The T-ILVAS successfully

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Table 1: Continued

Author, date, journal, country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Prospective cohort study (level 2a)	magnetically suspended impeller) was implanted into 6 sheep	1500 and 2000 rev/min the device pumped up to 8 l/min capturing all mitral flow		supported the systemic circulation without anticoagulation for up to 210 days
		Complications	There were no major complications: pump failure, thromboembolism, haemorrhage or driveline infection	One embolus was found in a sectioned kidney
Pereira *et al.*, 2010, Interact CardioVasc Thorac Surg, USA [15] Case report (level 4)	Two patients in whom recurrent GI bleeding during LVAD support with axial left ventricular assist device	Thromboembolic complications	None	Discontinuation of anti-thrombotic regimen for a year or more
Steinlechner *et al.*, 2009, Ann Thorac Surg, Austria [16] Prospective cohort study (level 2a)	Platelet function was assessed in 12 LVAD outpatients and 12 healthy matched volunteers using TEG platelet mapping, thromboelastometry, PFA-100 and a whole blood aggregometre (multiplate)	Anticoagulation protocol	Warfarin with INR target 2.5–3.5. Aspirin 100 mg/day	Multimodal antiplatelet monitoring with TEG ROTEM and the PFA-100 and multiplate showed impaired platelet function in patients with LVAD
		Hemostatic profile	Although antigen levels of von Willebrand factor were 80% higher in patients ($P < 0.001$), von Willebrand factor-ristocetin was subnormal in 5 of 12 patients. Ristocetin-induced aggregation was also threefold higher in volunteers ($P < 0.001$)	collagen adenosine diphosphate closure times were 2.5-fold longer in patients than in volunteers ($P < 0.001$), and 50% of patients had maximal collagen adenosine diphosphate closure time values
Tsukui *et al.*, 2007, J Thorac Cardiovasc Surg, USA [17] Retrospective cohort study (level 2b)	Sixty-four patients with LVAD: 22 HeartMate; 5 HM II; 19 Thoratec LVAD; 13 Novacor. 60 patients underwent BiVAD implantation with 57 Thoratec BiVADs and 3 HM LVAD + Thoratec RVAD	Anticoagulation	In all VAD implantation except with the HeartMate anticoagulation was started with dextran 40% at 25 ml/h 6 h after admission to the ICU if bleeding was less than 100 ml/h. Subsequently, heparin was started PTT 40–51 s for the first 72 h then PTT of 42–62 seconds. Warfarin was introduced on postoperative day (POD) 10 INR 2.5–3.5. Aspirin 81–325 mg and/or clopidogrel 75 mg daily was started 48 h after implantation	The risk of cerebrovascular accident (CVA) increases with a longer LVAD support period. Infection may activate platelet function and predispose the patient to a CVA. Antiplatelet dose was adjusted to maintain MA at TEG between 60 and 70 mm
		CVAs	31 patients (25%) had 48 CVAs. 60% of CVAs occurred within 4 months after implantation	42% of CVAs occurred in patients with infections

Continued

Table 1: Continued

Author, date, journal, country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
		Actuarial freedom from cerebrovascular accident at 6 months	75, 64, 63 and 33% with the HeartMate, Thoratec BVAD, Thoratec LVAD and Novacor, respectively	

PTT: partial thromboplastin time; BVAD: biventricular assist device; ADP: adenosine diphosphate; POD: post operative day.

aspirin and dipyridamole, reported an incidence of gastrointestinal (GI) bleeding events of 44.3%. Anticoagulant use was not statistically different between bleeders and non-bleeders, with an average INR at time of bleeding of 1.67 ± 0.53.

Stern *et al*. [3] similarly reported an incidence of GI bleeding of 40% in the HeartMate II (HM II) axial-flow LVAD, group versus 0% in the pulsatile one. The anticoagulation protocol consisted of a low-dose of aspirin and dipyridamole and warfarin (INR of 2.0–3.0). Interestingly, 3 bleeding patients uneventfully withheld warfarin for about four months.

Demirozu *et al*. [4], in a large series of 172 patients, supported with HM II and anticoagulated with warfarin aspirin and dipyridamole, reported a GI bleeding rate of 32%. They demonstrated the presence of an arteriovenous malformation in 31% of the bleeding patients.

Geisen *et al*. [5] demonstrated that their axial-flow LVAD patients developed impaired coagulation secondary to acquired von Willebrand syndrome (AvWS).

Crow *et al*. [6], in a multicenter prospective study, investigated the impact of continuous flow LVAD support on the haemostatic profile in 37 patients. All LVAD recipients developed AvWS after the device implantation, but only 10 had bleeding complications. The anticoagulation protocol consisted of warfarin (INR target 1.5–2.0) and aspirin. INR levels between bleeders and non-bleeders were similar. Point of care test for the evaluation of platelet function was not used. They conclude that the loss of high-molecular-weight von Willebrand factor multimers alone cannot predict bleeding risk.

Meyer *et al*. [7] showed the reversibility of AvWS in 26 patients supported with axial-flow LVAD implanted as bridge to transplantation after the removal of the device. During LVAD support they reported an incidence of bleeding of 0.17 per patient-year using warfarin (INR target 2.5 ± 0.5) and Aspirin 100 mg/day. If a patient was diagnosed with AvWS, aspirin was stopped. One patient had fatal mesenteric ischaemia. Platelet function analyser showed severe impairment in all patients on LVAD support.

Jennings *et al*. [8] reported that their outpatient HM II cohort (16 patients) spent 32% of the average time below the therapeutic INR range (2.0–3.0) with only one incidence of TIA and no incidence of GI bleeding episodes. The authors did not comment about antiplatelet therapy.

Slaughter *et al*. [9], showed that, despite high shear stresses associated with a high-speed axial flow pump, there was no effect on platelet activation, independently of length of support, antiplatelet and anticoagulation regimens used.

John *et al*. [10], in their series of 45 patients supported with HM II, successfully reduced the intensity of anticoagulation (avoiding postoperative heparin infusion, decreasing the therapeutic INR to 1.5–2.0 and introducing aspirin at 81 mg/day from post op day 2–3), without any increase in thromboembolic events.

Attisani *et al*. [11] successfully used a platelet aggregation test (PAT) to reduce the dose of antiplatelet in 14 patients supported with the INCOR LVAD and anticoagulated with warfarin (INR target 2.8–3.2). They showed that 82% required a dose of aspirin of 25 mg twice a day and 90% a dose of clopidogrel of 35 mg/day, to reduce the maximum aggregation <30%. They reported no GI bleeding episodes and a rate of major and minor thromboembolic events of 0.09 and 0.2 per patient-year, respectively.

Meuris *et al*. [12], in 10 patients supported with the INCOR LVAD implanted as bridge-to-transplantation, suggested the use of the low molecular weight heparin (LMWH) (1 mg/Kg twice daily) and triple antiplatelet therapy (aspirin at 80 mg two times daily; clopidogrel at 75 mg daily; and dipyridamole 75 mg three times daily) as an alternative to oral anticoagulants. PAT was used to reduce platelet aggregation levels to at least 30%. They reported 1 severe stroke with concomitant fatal intracranial bleeding and 4 Thrombus-related pump dysfunction.

Copeland *et al*. [13], similarly in children with LVAD used IV heparin associated with point-of-care titrate antiplatelet therapy consisting of: Aspirin 2–10 mg/kg/min increased in larger children by 162–325 mg for each 100 000 platelets above 150 000; dipyridamole, IV at 0.1 mg/kg/h in children <6 years old, 50 mg (age 6–10 years) or 100 mg (>10 years) by mouth every 6 h; pentoxifylline 400 mg per os three times daily(age > 6). This experience was worrisome, with 20% incidence of reoperation for bleeding and 25% of stroke (2 fatal).

Saito *et al*. [14], in an animal model, successfully supported the systemic circulation with continuos flow LVAD without any anticoagulation up to 210 days.

Pereira *et al*. [15] reported 2 axial-flow LVAD patients who stopped anti-thrombotic therapy for more than a year because of recurrent GI bleeding episodes, without any thrombotic complications.

Steinlechner *et al*. [16], simultaneously used thrombelastography (TEG), rotation thromboelastometry (ROTEM), platelet function analyser (PFA-100) and multiplate, on 12 patients supported with

continuous flow LVAD. They showed markedly impaired platelet function independently from the effect of the anticoagulation therapy with warfarin (INR target 2.5–3.5) and aspirin 100 mg/day.

Tsukui *et al.* [17], in a retrospective analysis of 124 patients with axial-flow LVAD and biventricular assist device (BIVAD) anticoagulated with warfarin (INR 2.5–3.5) and aspirin (81–325 mg/day) e/o clopidogrel 75 mg/day to maintain the maximum amplitude (MA) on the TEG between 60–70 mm, reported 25% of cerebrovascular accidents (CVAs), 42% happening in patients with infections. The mean MA in the presence of infection (63.6 mm) was higher than that in the absence of infection (60.7 mm) ($P = 0.0309$).

CLINICAL BOTTOM LINE

There is a substantial alteration of the prothrombotic profile in patients with axial-flow LVADs. These abnormalities appeared to be reversible with the removal of the device and are likely to be responsible for the high incidence of non-surgical bleeding episodes reported. Warfarin seems to offer a lower thromboembolic risk compared with unfractioned heparin or LMWH. There are reports that suggest that managing axial-flow LVAD without anticoagulation, after major bleeding complications, is possible, but in all probability these papers are subject to publication bias as poor out-comes are unlikely to have been reported. All patients with axial-flow LVAD showed severely impaired platelet function at point of care tests. The use of warfarin (INR target 2.5), in association with aspirin at 100 mg/day, or with point-of-care tests titrated antiplatelet therapy to inhibit 70%, seems to have the best bleeding-thrombosis, and in many cases a very small dose of aspirin of 25 mg twice a day and a dose of clopidogrel of 35 mg/day, were sufficient to achieve a reduction of the maximum aggregation to less than 30%. Finally, we would like to emphasize that such recommendations are addressed only to patients with axial-flow LVAD.

Conflict of interest: none declared.

REFERENCES

[1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. Interact CardioVasc Thorac Surg 2003;2:405–9.

[2] Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A *et al.* Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol 2010;56:1207–13.

[3] Stern DR, Kazam J, Edwards P, Maybaum S, Bello RA, D'Alessandro DA *et al.* Increased incidence of gastrointestinal bleeding following implantation of the HeartMate II LVAD. J Card Surg 2010;25:352–6.

[4] Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B *et al.* Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. J Heart Lung Transplant 2011;30:849–53.

[5] Geisen U, Heilmann C, Beyersdorf F, Benk C, Berchtold-Herz M, Schlensak C *et al.* Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. Eur J Cardiothorac Surg 2008;33:679–84.

[6] Crow S, Chen D, Milano C, Thomas W, Joyce L, Piacentino V III *et al.* Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg 2010;90:1263–9.

[7] Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A *et al.* Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail 2010;3:675–81.

[8] Jennings D, McDonnell J, Schillig J. Assessment of long-term anticoagulation in patients with a continuous-flow left-ventricular assist device: a pilot study. J Thorac Cardiovasc Surg 2011;142:e1–2.

[9] Slaughter MS, Sobieski MA II, Graham JD, Pappas PS, Tatooles AJ, Koenig SC. Platelet activation in heart failure patients supported by the HeartMate II ventricular assist device. Int J Artif Organs 2011;34:461–8.

[10] John R, Kamdar F, Liao K, Colvin-Adams M, Miller L, Joyce L *et al.* Low thromboembolic risk for patients with the Heartmate II left ventricular assist device. J Thorac Cardiovasc Surg 2008;136:1318–23.

[11] Attisani M, Centofanti P, La Torre M, Campanella A, Sansone F, Rinaldi M. Safety and effectiveness of low dosing of double antiplatelet therapy during long-term left ventricular support with the INCOR system. J Artif Organs 2010;13:202–6.

[12] Meuris B, Arnout J, Vlasselaers D, Schetz M, Meyns B. Long-term management of an implantable left ventricular assist device using low molecular weight heparin and antiplatelet therapy: a possible alternative to oral anticoagulants. Artif Organs 2007;31:402–5.

[13] Copeland H, Nolan PE, Covington D, Gustafson M, Smith R, Copeland JG. A method for anticoagulation of children on mechanical circulatory support. Artif Organs 2011;35:1018–23.

[14] Saito S, Westaby S, Piggott D, Katsumata T, Dudnikov S, Robson D *et al.* Reliable long-term non-pulsatile circulatory support without anticoagulation. Eur J Cardiothorac Surg 2001;19:678–83.

[15] Pereira NL, Chen D, Kushwaha SS, Park SJ. Discontinuation of antithrombotic therapy for a year or more in patients with continuous-flow left ventricular assist devices. Interact CardioVasc Thorac Surg 2010;11:503–5.

[16] Steinlechner B, Dworschak M, Birkenberg B, Duris M, Zeidler P, Fischer H *et al.* Platelet dysfunction in outpatients with left ventricular assist devices. Ann Thorac Surg 2009;87:131–7.

[17] Tsukui H, Abla A, Teuteberg JJ, McNamara DM, Mathier MA, Cadaret LM *et al.* Cerebrovascular accidents in patients with a ventricular assist device. J Thorac Cardiovasc Surg 2007;134:114–23.