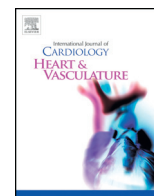


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## Antithrombotic therapy in ventricular assist device (VAD) management: From ancient beliefs to updated evidence. A narrative review☆

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### ABSTRACT

Platelets play a key role in the pathogenesis of ventricular assist device (VAD) thrombosis; therefore, antiplatelet drugs are essential, both in the acute phase and in the long-term follow-up in VAD management. Aspirin is the most used agent and still remains the first-choice drug for lifelong administration after VAD implantation. Anti-coagulant drugs are usually recommended, but with a wide range of efficacy targets. Dual antiplatelet therapy, targeting more than one pathway of platelet activation, has been used for patients developing a thrombotic event, despite an increased risk of bleeding complications. Although different strategies have been attempted, bleeding and thrombotic events remain frequent and there are no uniform strategies adopted for pharmacological management in the short and mid- or long-term follow up. The aim of this article is to provide an overview of the evidence from randomized clinical trials and observational studies with a focus on the pathophysiologic mechanisms underlying bleeding and thrombosis in VAD patients and the best antithrombotic regimens available.

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### 1. Introduction

Depending on the definition applied, the prevalence of heart failure (HF) is approximately 1–3% in the adult population, rising to 8–10% for subjects aged 75 years or older [1, 2]. In patients acutely hospitalized, HF is still associated with very poor medium-term prognosis, with all-cause death being approximately 20% and all-cause re-hospitalization rate up to 50% at 1-year follow up [3].

Permanent implantable ventricular assist devices (VADs) are a consolidated alternative to heart transplantation (HTx) for ineligible patients with end-stage HF (destination therapy). VADs are currently implanted also in patients on waiting list for HTx (as bridge to transplantation) or needing evaluation for candidacy in order to achieve end-organ recovery (bridge to candidacy) [1].

VADs can be categorized based on their mechanism of blood propulsion. First generation VADs were pulsatile devices mimicking the natural heart flow dynamic, whereas second- and third-generation devices provide continuous flow (with axial or centrifugal design) [4].

Despite technological improvements (greater durability and easier placement) with the continuous flow design, bleeding and thromboembolism, as well as pump thrombosis, remain frequent complications that may affect the long-term outcome of patients on VAD [5–7]. Indeed, only 30% of patients remain free from bleeding or thromboembolic complications after 1 year from VAD implantation [8].

The event rate per patient-year is  $\approx 0.40$  and  $0.06$  for non-gastrointestinal and gastrointestinal major bleeding [9],  $0.04$  to  $0.09$  for pump thrombosis [10], and  $0.08$  for hemorrhagic or ischemic stroke [9]. The clinical consequences of thrombotic and bleeding complications can be devastating, with ischemic and hemorrhagic stroke remaining among the most common causes of death in these patients (adjusted hazard ratio  $6.1$ ; 95% CI,  $4.6$ – $7.9$ ) [11]. Even if an increase in pump thrombosis reported in previous studies [12–14] has been mitigated in recently published trials [15, 16], pump thrombosis may be a vexing problem because of older patients and longer duration of life after implantation. Device manufacturers usually suggest the use of a specific antiplatelet or anticoagulant agent, without any strong evidence

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supporting their indication. Therefore, the antithrombotic therapy in patients with VADs is still evolving to better face the fine balance between bleeding and thrombosis.

The aim of the present review is to summarize the available evidence about the pathophysiological mechanisms contributing to bleeding and thrombosis in VAD patients, the managements that are usually adopted and the future lines of research.

## 2. Search strategy

Databases including PubMed, OVID, SCOPUS, CINAHL, Cochrane and Web of Science were searched from database inception through to 28 March 2018, using the predefined search terms “assist device”, “thrombosis”, “bleeding”, “antiplatelet therapy”, “anticoagulation”, “antithrombotic management” using Boolean logic operators (AND) and (OR), with exploded headings. Search of the literature was performed without predefined “timeframe” for published articles. No language and study type limits were applied. Reference lists of selected publications were also analyzed for additional linking studies.

## 3. Pathophysiology of thrombosis and bleeding in LVAD patients

Thrombus formation is a dynamic process that is regulated by components of the hemostatic system, which, under physiological conditions, form blood clots that limit blood loss from damaged vessels [15]. Platelet reactions with the solid surfaces of damaged blood vessels depend on the presence of plasma von Willebrand Factor (vWF) activity [17]. vWF is a multimeric glycoprotein manufactured by the endothelial cells, where it is constitutively released into the circulation and stored into the Weibel-Palade bodies, from where it can be rapidly released upon stimulation [17, 18]. vWF is stored also in the  $\alpha$ -granules of megakaryocytes/platelets, from which it is released only upon platelet activation [17, 18]. vWF circulates in the plasma and it is critical for primary hemostasis, being essential for platelet adhesion to the subendothelium of damaged blood vessel, platelet activation and platelet aggregation [19]. Furthermore, it is required to control the formation of vascular network [19].

Rheological variables play a role in thrombus formation, by affecting the ability of platelets to hook up to adhesive proteins that are exposed on the vessel wall (platelet adhesion) or are bound on the surface of other platelets (platelet aggregation) [17]. Shear stress is defined as the force for area unit between the blood laminae. The normal physiologic range of fluid shear stress within the cardiovascular system is 15 to 40 dyne/cm<sup>2</sup> (1.5–4 Pa) [20]. Under physiologic shear stress, vWF undergoes a conformational elongation from a globular state to an extended chain conformation with exposure of binding sites for the platelet glycoprotein complex GpIb/IX/V and various subendothelial constituents [21]. The interaction of vWF with platelet GpIb/IX/V causes platelet activation, secretion of ADP, activation of the GpIb-IIIa receptor and platelet aggregation. However, the same conformation elongation exposes the disulfide bonds of vWF multimers, site of enzymatic degradation cleavage of large, active vWF multimers into small, nonactive vWF fragments by the vWF protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [22–25]. Therefore, the pathogenesis of bleeding and thrombosis depends on the imbalance between these pro-hemostatic and anti-hemostatic factors.

### 3.1. Thrombosis

Each VAD has a specific mechanism of blood propulsion, able to produce different hemodynamic profiles associated with changing degrees of pulsatility, turbulence and shear stress. The shear stress that is generated within VADs ranges between 20 and 500 Pa [26, 27].

Shear stress acts as chemical agonists, showing dose and time-response characteristics. The elongated vWF formed under conditions

of high shear stress becomes procoagulant through accumulation of contact pathway factors. Accordingly, placement of VADs has been associated with persistent generation of activated contact proteins (FXIa and its co-localized activator FXIIa), that accumulate on the vWF as they form under pathological flow [28] and are absorbed to the surface of VADs via the *Vroman* effect (according to the original theory, the small molecules are the first to be absorbed on a surface, but they are gradually stifled by proteins with greater affinity) [29]. The threshold evoking a specific response in terms of platelet adhesion and aggregation may change over time depending on the specific interactions between platelets and solid surface and the exposition time [17].

Platelet aggregation induced under supraphysiologic shear stress, as usually occurred in patients with VAD, has peculiar characteristics [30–33]. Thrombelastographic analyses have demonstrated that contact protein pathway activation results in a thrombus that develops strength at a significantly faster rate and that takes significantly longer to lyse than thrombi generated by tissue factor initiated coagulation, by more efficient activation of the thrombin-activatable fibrinolysis inhibitor [34]. It is well known that vWF stress-stimulated aggregation is little affected by inhibition of cyclooxygenase by acetylsalicylic acid, whereas it is inhibited by fibrinolytic agents [35,36]. Therefore, ideally, agents acting on ADP activity (as P2Y<sub>12</sub> inhibitors), blocking GP Ib or GP IIb/IIIa or acting on the fibrinolytic system might be suitable therapeutic target to decrease thrombosis rate in VAD patients.

In experimental studies analyzing platelet-rich plasma under conditions of high shear stress, >50% of activation and aggregation caused by the interaction of vWF with platelet GP Ib could be inhibited by blocking the action of P2Y<sub>12</sub> [37].

Similarly, studies *in vitro* have demonstrated that, under supraphysiologic shear stress, phosphodiesterase (PDE) 3 inhibitors suppress the platelet thrombus formation initiated by the interaction of the platelet receptor GpIb/V/IX with the vWF [38]. The only selective PDE-3 inhibitor available is cilostazol. Several observations conducted *in vitro* have confirmed the favorable profile of cilostazol in reducing platelet activation under both constant and dynamic device-related conditions [33, 39, 40]. However, as recently reported, FDA has contraindicated the use of cilostazol for patients with any degree of heart failure [33, 41]. Dipyridamole is both a PDE-3 and -5 inhibitor, but studies *in vitro* have revealed its decreased activity on platelet inhibition under conditions of high shear stress [33].

Finally, a further mechanism leading to thromboembolic complications in VAD patients could be the heat stress. Investigations in this field have revealed hemoconcentration, activation of coagulation with decreased clotting time and increased clot strength and thrombin and D-dimer release [42]. Heat stress may act promoting activation of several inflammatory pathways and inducing the release of chemical agonists as epinephrine. This explains why in this context inhibition of the cyclo-oxygenase enzymes by acetylsalicylic acid, decreasing production of prostaglandins and other inflammatory mediators, is of potential benefit [43].

### 3.2. Bleeding

On the opposite site of the coin, shear stress may have a role in bleeding diathesis. Acting on the weaker disulfide bonds of vWF multimers, shear stress could tear apart vWF monomers. In parallel, supraphysiologic shear stress is the major mechanism leading to enzymatic degradation cleavage of large, active vWF multimers into small, nonactive vWF fragments by the vWF protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [30]. As a result, an acquired vWF deficiency develops, thus significantly affecting sprouting angiogenesis. vWF is a ligand for the integrin  $\alpha v\beta 3$ , involved in the regulation of the directionality of cellular migration [22]. Furthermore, vWF drives the formation of Weibel-Palade bodies, which stores regulators of angiogenesis and inflammation including angiotensin-2.

Decreased levels of vWF induce internalization and increased degradation of  $\alpha v\beta 3$  and increased release of angiopoietin-2 [22–25]. Dysregulated angiopoietin-2 may lead to endothelial cells proliferation and migration throughout the vascular endothelial growth factor (VEGFR)-dependent pathways, with increased neo-angiogenesis and vascularization [18, 22–25, 44].

Increased angiopoietin-2 release further induces  $\alpha v\beta 3$  internalization, amplifying cellular proliferation and migration [25]. These multiple cross-talking pathways results in dysplastic vessels and arterio-venous malformations predisposing patients with a VAD to bleeding events [45].

Moreover, diminished pulsatility and increased intraluminal pressure have also been postulated to induce distention of submucosal venous plexus and microvascular perfusion injury of the small bowel [45].

Finally, patients with blood type O have been noted to have lower baseline levels of vWF compared with other blood groups, though the precise mechanism of this regulation remains unknown [46]. However, these slight differences are unlikely to be clinically significant, as reported in studies performed in patients undergoing coronary artery bypass [46]. Moreover, in patients with centrifugal devices, the vWF antigen and vWF activity did not differ among individuals with blood group “O” compared to the other blood groups [47].

These complex relationships (Fig. 1) acknowledge why it is so difficult to find a proper management in patients with VAD support. Summarizing the available evidences from prior published work is challenging because different pumps and center-specific protocols have been adopted, limiting our ability to definitively integrate the available information. Finally, it should always be taken into consideration that risk factors contributing to pump thrombosis are related not only to the pump itself, but even to the patient pre-existing conditions (atrial fibrillation, preexistent thrombus, uncontrolled hypertension, hypercoagulable state as in course of anti-phospholipid antibody syndrome, acute heparin-induced thrombocytopenia or active infection) and patient’s compliance with regular medications drugs [48].

#### 4. Antithrombotic strategies

##### 4.1. Secondary prevention of thromboembolic events after VAD implantation: anticoagulant treatment

According to the International Society of Heart and Lung Transplantation guidelines [49] supported by the American Heart Association [50], patients with VAD should receive anti-coagulation with warfarin to maintain an International Normalized Ratio (INR) within a range as specified by each device manufacturer; aspirin (81–325 mg daily) and other antiplatelet drugs may be used in addition to warfarin according to the recommendations of specific device manufacturers, but these indications are mostly based on experts’ opinion [49, 50].

Table 1 summarizes the most commonly implanted devices, their specific rheology and the recommended antithrombotic regimen by each device manufacture.

In the 2012 Rossi et al. published a review including 538 patients with axial-flow VAD (HeartMate II, Jarvik 2000, INCOR, Thoratec assist device). Search strategies involved 758 papers retrieved from 1950 to March 2012. Pooling the results of the 17 papers included in the final analysis, the authors suggested that use of warfarin (INR target 2.5), in association with aspirin at 100 mg/day could be considered the best option [51].

In 2015, Bauman et al. published a systematic review focused on the antithrombotic therapy for left ventricular assist devices (LVADs), both axial and centrifugal, in adults [52]. The authors screened 1276 articles identified throughout database searching and other sources. One-hundred and four articles were assessed for eligibility and 24 studies were included in the qualitative synthesis, reporting outcomes of 2784 LVADs with a range of implantation time between 1 day and 2823 days. Almost all of the studies were deemed of moderate quality, as they were mostly retrospective and without a comparison group.

The different antithrombotic strategies adopted and the lack of a standardized definition of bleeding between studies limited the ability to compare antithrombotic regimens. Major bleeding, according to each study definition, was reported in 30% of patients. Stroke and pump thrombosis were reported in 6% and 5% of patients. Death was reported in 20% of patients. The most frequent causes of death were multiorgan failure (31%), infections (15%), ischemic stroke (13%), right heart failure (11%), bleeding (10%), mechanical failure of the device (3%), with fatal bleedings and fatal thromboembolic complications showing similar incidences. The authors concluded that lack of effective INR control may be associated with bleeding and thromboembolic complications and that the optimal antithrombotic regimen in LVAD patients remains undetermined. Moreover, the role of antiplatelet therapy during LVAD support was still unclear.

The most recent evidences of the current literature show that differences in markers of hemolysis and coagulation activation may exist according to the specific VAD implanted [14–16, 53]. Actually, the improved hemocompatibility achieved with the new generation devices has led to the conclusion that low-intensity anticoagulation (INR range 1.5–1.9) could be a safe and effective strategy in patients closely monitored with new magnetically levitated centrifugal-flow circulatory pump, associated with a short term (six weeks post-implantation) antiplatelet strategy [14, 15, 54]. However, further studies on larger samples are needed to confirm this hypothesis.

##### 4.2. Secondary prevention of thromboembolic events after VAD implantation: antiplatelet treatment

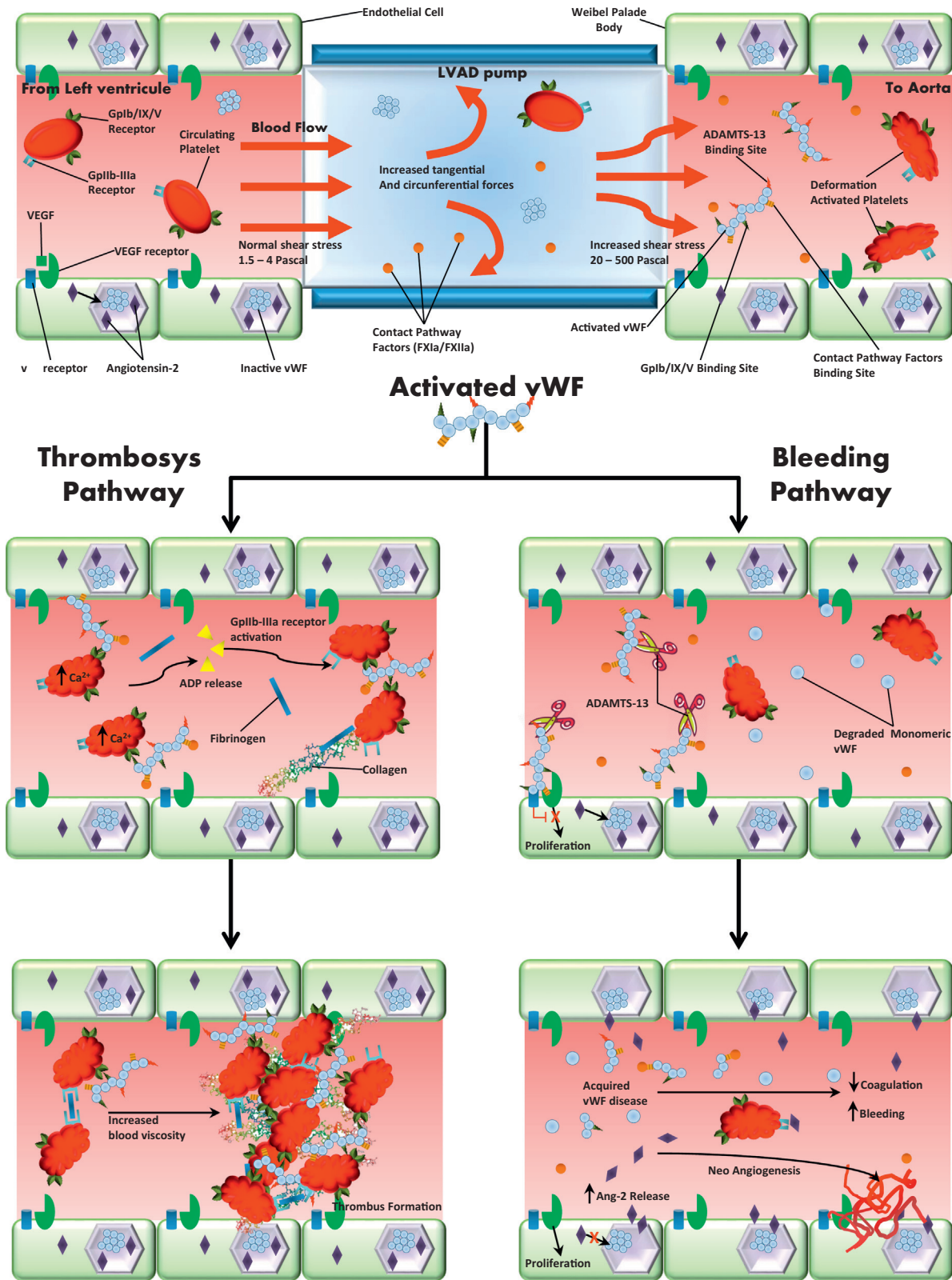
Even if **aspirin** is commonly recommended and used as the first-line therapy in patients with LVAD since the first clinical experiences [55], mechanisms of platelet activation in VADs patients (shear-induced platelet aggregation) make the efficacy of aspirin questionable. Furthermore, an experimental study conducted in a small sample of patients with external VAD implantation [56], has documented a non-trivial risk of aspirin hyporesponsiveness, defined by persistent platelet aggregation in 26% of the patients under arachidonic acid exposition. In this study patients on VADs support experienced a persistent inflammatory status as expressed by elevated fibrinogen levels and circulating von Willebrand Factor values. Mechanisms for aspirin hyporesponsiveness are potentially multiple in VAD patients [17, 57–60]: a) an increase in platelets turnover may overcome the effect of aspirin on thromboxane A<sub>2</sub> synthesis [57]; b) chronic inflammatory status may promote the cyclooxygenase-2 isoform activity, that is less sensible to aspirin acetylation [58]; c) platelet adhesion and activation under high shear stress are poorly sensitive to aspirin [59].

**Clopidogrel** has been suggested in the case of aspirin intolerance [10] or according to specific indications, mostly in the context of recent thromboembolic events [61]. However, the antiplatelet response to clopidogrel, performed with the platelet function analyzer-100 system and the vasodilator-stimulated phosphoprotein phosphorylation assay, is highly variable, with almost 50% of patients showing insufficient anti-platelet response [53].

**The combination of dipyridamole** and aspirin is associated with a decreased relative and absolute risk of thromboembolic events in VAD patients of 50% and 9%. However, these data have been reported only in few experiences with axial devices [54] and are inconsistent in the general VAD population.

**Prasugrel and ticagrelor**, P2Y<sub>12</sub> antagonists with more predictable pharmacokinetics than clopidogrel, have not been routinely prescribed in patients with VAD likely for fear of an unacceptable high risk of bleeding events. One small case-series suggested a positive role of ticagrelor in patients with suspected LVADs thrombosis [62]. However, on the basis of our clinical experience, the generalizability of these optimistic results is questionable [63].





**Fig. 1.** Thrombosis and bleeding pathways in patients with ventricular assist device. Under physiologic shear stress, vWF undergoes a conformational elongation from a globular state to an extended chain conformation with exposure of binding sites for the platelet glycoprotein complex GpIb/IX/V and various subendothelial constituents. This interaction causes platelet activation, secretion of ADP, activation of the GpIb-IIIa receptor and platelet aggregation (central box and box on the top left). However, the same conformation elongation exposes the disulfide bonds of vWF multimers and allows the inactivation process by the vWF protease ADAMTS-13 (box on the top right). Placement of VADs may amplify these processes, increasing shear stress and promoting activated contact proteins release. Therefore, the increased activation of vWF may explain the dual pathway activation: increased thrombosis by platelets activation and contact proteins system (pathway on the left) and bleeding diathesis throughout ADAMTS-13 activation and acquired vWF disease (pathway on the right).

**Table 1**

Ventricular assist devices usually implanted in our center and antithrombotic strategies suggested for secondary prevention of thromboembolic events.

Device	Weight	Type of flow	Range Speed	Material motor can	Material inflow canula	Dose aspirin	Range OAC (INR)
HM II	281 g	Axial	8000–15,000	Titanium	Titanium	100 mg	2–3
HM III	180 g	Centrifugal	4000–9000	Titanium	Titanium	100 mg	2–3
HW	160 g	Centrifugal	2400–3200	Titanium	Titanium	300 mg	2,5–3

HM: HeartMate, Thoratec Corporation; HW: HeartWare ventricular assist device system, HeartWare.

#### 4.3. Antithrombotic therapy in patients with thromboembolic events

Thrombolysis has been evaluated in patients with pump thrombosis according to local algorithms based on single-center experiences. However, a systematic review and metaanalysis has not documented a significant increased rate of success in patients with pump thrombosis treated with thrombolytic regimens compared to nonthrombolytic pharmacological management [64]. An extensive review of this issue is out of the present revision.

**Glycoprotein IIb/IIIa inhibitors** have been evaluated as an alternative to fibrinolysis in patients with suspected device thrombosis. However, patients with confirmed events, failed to have a clinically measurable response to therapy [65, 66].

Direct thrombin inhibitors (DTI) might have a strong rationale in this setting.

**Bivalirudin** is a specific and reversible DTI used in clinical practice since the early '90s, as an alternative medication to heparin, during percutaneous coronary intervention (PCI) [67]. DTIs are better pharmacological tools, compared to unfractionated heparin (UFH). Their advantages include being independent of antithrombin III levels, better bioavailability, and capacity to inhibit both soluble and clot-bound thrombin, which reduces clot formation and propagation. Furthermore, DTIs inhibit thrombin-induced platelet activation [68].

About 20% of bivalirudin is excreted unchanged in the urine. Drug elimination depends on glomerular filtration rate; therefore, the half-life is 25–30 min in healthy patients but is increased to 1 h in severe renal disease and is estimated to be 3.5 h in end-stage renal disease requiring hemodialysis. Intravenous administration of bivalirudin produces measurable anticoagulation within few minutes with linear increases in prothrombin time, activated partial thromboplastin time (aPTT), activated clotting time (ACT) and thrombin time [68].

Bivalirudin has been approved for use in patients undergoing PCI with or without prior treatment with unfractionated heparin (UFH) and in patients with heparin-induced thrombocytopenia (HIT) and current guidelines support its use in acute coronary syndrome patients [69]. In patients undergoing PCI, it is administered as a bolus of 0.75 mg/kg, followed by a continuous infusion at 1.75 mg/kg/h for the entire procedure. The infusion dose should be reduced in patients with renal insufficiency: 1 mg/kg/h for patients with creatinine clearance <30 ml/min, and 0.25 mg/kg/h for patients in hemodialysis [70]. Mueller et al. reported the successful use of bivalirudin therapy for prevention of hemofilter occlusion during continuous veno-venous hemofiltration (CVVH) in a patient with hepatic and renal dysfunction. The bivalirudin dose was 0.09 mg/kg/h. No bleeding complications were noted [71].

Preliminary experiences in patients with VAD implantation have been favorable. In 2014 Pieri et al. performed a study on 12 consecutive patients who underwent VAD implantation and received primary anticoagulation with Bivalirudin: the starting dose was 0.025 mg/kg/h, the median dose was 0.04 ± 0.026 mg/kg/h and median duration of therapy was 5 days. Patients never received heparin during hospitalization nor had a prior diagnosis of HIT. No patient had thromboembolic complications or major bleeding events and the authors concluded that bivalirudin should be a valuable alternative anticoagulant therapy in VAD patients. Other clinical experiences have confirmed the safety profile in this setting [72].

Evidences to support the use of a DTIs in LVAD are mostly anecdotal. In the small case series reported by Lynne et al. bivalirudin was used as an alternative to heparin in six hemodynamically stable patients admitted to hospital for suspected LVAD thrombosis. The starting dose was between 0.03 and 0.15 mg/kg/h and the maintenance dose ranged from 0.04 to 0.23 mg/kg/h. In these cases, bivalirudin was relatively safe and effective for the treatment of LVAD thrombosis even if a high rate of recurrence was showed [73].

**Argatroban** is another intravenous DTI used in cases of suspected LVAD thrombosis. It is metabolized by the liver, while it has no renal clearance. In comparison with bivalirudin, argatroban has higher affinity for thrombin with a more effective inhibition of clot-bound thrombin: the dose usually employed is 2 µg/kg/min, aiming at prolonging aPTT to 1.5–3 times the baseline values. Argatroban also prolongs the PT, thus interfering with laboratory monitoring of warfarin, when the two drugs are co-administered [74].

**Dabigatran**, an oral DTI, have been evaluated in LVAD patients with promising results [75]. However, a recent randomized controlled trial showed an excess of thromboembolic events in dabigatran-treated patients compared to phenprocoumon-treated patients [76].

Even if the dual pathway therapy with direct oral anticoagulant agents combined with P2Y12 inhibitor appears promising in patients with acute coronary syndromes, based on the results of recent randomized trials on dabigatran and rivaroxaban [77, 78], this strategy has not been tested in LVAD patients. Moreover, in view of the unfavorable results in patients with mechanical valves, this option deserves ad hoc well-designed trial.

In our clinical experience all the pharmacological strategies above reported have been attempted in different clinical scenarios. Bivalirudin has been used with a good profile of safety and efficacy in patients at higher risk for both the conditions (suspected pump thrombosis and hemorrhagic events, even cerebral hemorrhagic foci).

## 5. Conclusions

Antithrombotic management in VADs patients is based on ancient protocols without strong experimental evidence. Large clinical trials with standardized laboratory methods and well-defined protocols are needed in order to evaluate the different antiplatelet and anticoagulant drugs available, suggesting therapeutic strategies to overcome the risk of thrombotic and bleeding events.

## Disclosures

None of the authors report any conflict of interest with the specific subject of the study.

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