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ORIGINAL ARTICLE

Platelet reactivity is associated with pump thrombosis in patients with left ventricular assist devices

David Mutschlechner[1,2,3] | Maximilian Tscharre[4,5] | Franziska Wittmann[6] | Daniela Kitzmantl[7] | Thomas Schlöglhofer[6] | Patricia Pia Wadowski[7] | Günther Laufer[8] | Beate Eichelberger[9] | Silvia Lee[7] | Dominik Wiedemann[10] | Simon Panzer[9] | Daniel Zimpfer[6] | Thomas Gremmel[1,2,3,7]

[1]Department of Internal Medicine I, Cardiology and Intensive Care Medicine, Landesklinikum Mistelbach-Gänserndorf, Mistelbach, Austria

[2]Institute of Cardiovascular Pharmacotherapy and Interventional Cardiology, Karl Landsteiner Society, St. Pölten, Austria

[3]Karl Landsteiner University of Health Sciences, Krems, Austria

[4]Department of Internal Medicine, Cardiology and Nephrology, Landesklinikum Wiener Neustadt, Wiener Neustadt, Austria

[5]Institute of Vascular Medicine and Cardiac Electrophysiology, Karl Landsteiner Society, St. Pölten, Austria

[6]Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

[7]Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria

[8]Division of Cardiac Surgery, Department of Surgery, Medical University Graz, Graz, Austria

[9]Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria

[10]Department of Cardiac Surgery, Universitätsklinikum St. Pölten, St. Pölten, Austria

Correspondence
Thomas Gremmel, Department of Internal Medicine I, Cardiology and Intensive Care Medicine, Landesklinikum Mistelbach-Gänserndorf, Liechtensteinstraße 67, 2130 Mistelbach, Austria.
Email: thomas.gremmel@mistelbach.lknoe.at

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Abstract

Background: Patients with left ventricular assist devices (LVADs) are treated with a potent antithrombotic regimen to prevent pump thrombosis and thromboembolism. High on-treatment residual platelet reactivity (HRPR) is associated with ischemic outcomes in cardiovascular disease.

Objectives: In the current study, we investigated the prevalence and clinical impact of HRPR in stable LVAD patients.

Methods: Pump thrombosis, bleeding events, and death were assessed in 62 LVAD patients (19 HeartWare HVAD [Medtronic] and 43 HeartMate 3 [Abbott]) during a 2-year follow-up. Platelet aggregation was measured by multiple electrode aggregometry, and HRPR was defined as arachidonic acid (AA)–inducible platelet aggregation of ≥21 aggregation units. Soluble P-selectin was determined by enzyme-linked immunosorbent assay.

Results: Three patients (4.8%) had pump thrombosis and 10 patients (16.1%) suffered a bleeding complication. AA-inducible platelet aggregation was significantly higher in patients with pump thrombosis ($P = .01$), whereas platelet aggregation in response to adenosine diphosphate (ADP) and thrombin receptor–activating peptide (TRAP) was comparable between patients without and those with pump thrombosis (both $P > .05$). Platelet aggregation in response to AA, ADP, and TRAP was similar in patients without and with a bleeding event (all $P > .05$). HRPR was detected in 29 patients (46.8%) and was associated with significantly higher platelet aggregation in response to AA, ADP, and TRAP as well as higher levels of soluble P-selectin compared with patients without HRPR (all $P < .05$). All pump thromboses occurred in patients with HRPR (3 vs 0; $P = .06$) and HVAD.

Conclusion: Platelet reactivity is associated with pump thrombosis in LVAD patients. HRPR may represent a risk marker for pump thrombosis, particularly in HVAD patients.

KEYWORDS
bleeding complications, heart failure, high on-treatment residual platelet reactivity, left ventricular assist devices, pump thrombosis

Essentials

- Platelet reactivity is linked to ischemic and bleeding events in cardiovascular disease.
- Outcomes and platelet reactivity were assessed in left ventricular assist device patients.
- Platelet reactivity is associated with pump thrombosis in left ventricular assist device patients.
- High on-treatment residual platelet reactivity may represent a risk marker for pump thrombosis.

1 | INTRODUCTION

Left ventricular assist devices (LVADs) have significantly improved the survival of patients with terminal heart failure over the last decades [1]. To prevent activation of the coagulation system due to the artificial surfaces, LVAD patients are treated with a potent antithrombotic regimen including a vitamin K antagonist (VKA) and aspirin [2,3]. Despite recent device innovations, LVAD patients remain at an increased risk of thromboembolic events [4].

Low-dose aspirin prevents platelet aggregation via inhibition of cyclooxygenase-1 and thereby inhibition of thromboxane A2 formation [5]. However, previous studies have shown wide interindividual variations of aspirin-mediated antiplatelet activity in different platelet function tests such as multiple electrode aggregometry (MEA) or light transmission aggregometry [6–10]. In recent years, several studies investigated the impact of high on-treatment residual platelet reactivity (HRPR) on cardiovascular events in different patient cohorts [11–13]. Thereby, studies and meta-analyses have shown an association of HRPR with the occurrence of ischemic outcomes [14–16]. In patients undergoing percutaneous coronary intervention (PCI) with stent implantation, HRPR was established as a risk factor for stent thrombosis and death [11]. In contrast, HRPR was found to be inversely correlated with bleeding events in patients with coronary artery disease (CAD) [12].

The prevalence of HRPR and its impact on thrombotic and bleeding outcomes in LVAD patients is unknown. We therefore investigated the prevalence and possible clinical impact of HRPR in a cohort of stable LVAD patients treated with a VKA and low-dose aspirin.

2 | METHODS

2.1 | Study population

The study cohort has been described previously [2]. The present study was monocentric and prospective with 62 LVAD patients (HeartWare HVAD [Medtronic] and HeartMate 3 [HM3; Abbott]) recruited between January 2018 and October 2020. LVAD indications were treatment of advanced heart failure as a bridge to transplantation, bridge to candidacy for transplantation, or destination therapy. Patients were recruited at the outpatient clinic of the Department of Cardiac Surgery, Medical University of Vienna. All patients were in a stable condition, and LVAD implantation was performed ≥3 months before recruitment. The antithrombotic regimen in all patients consisted of low-dose aspirin (HVAD, 200 mg daily; HM3, 100 mg daily) and the VKA phenprocoumon at a target international normalized ratio of 2.0 to 2.5 [2].

The exclusion criteria were known aspirin intolerance (allergic reactions or history of bleeding events), known bleeding disorders, known defects in thrombocyte function, a platelet count of <100.000 or >450.000/μL, a hematocrit level of <30%, acute or chronic infection, malignant paraproteinemia, myeloproliferative disorders, severe hepatic failure, and a major surgical procedure within 7 days before enrollment. In fact, none of the included patients underwent a surgical procedure within 3 months before platelet function testing [2].

The study protocol was in accordance with the criteria of the Declaration of Helsinki and has been approved by the Ethics Committee of the Medical University of Vienna (1769/2018). All study participants gave their written informed consent.

2.2 | Blood sampling

Blood was drawn from an antecubital vein with a 21-gauge butterfly needle (0.8 mm × 19 mm; Greiner Bio-One), as previously described [1]. To avoid procedural deviations, all blood samples were taken by the same physician (M.T.) by applying a light tourniquet that was immediately released, and the samples were mixed by gently inverting the tubes. Whole blood was drawn into 3.2% sodium citrate tubes (Greiner Bio-One) and centrifuged immediately after collection (1500 × *g* at 4 °C for 15 minutes), and the resulting plasma samples were stored at −80 °C until further measurements. Platelet function testing was performed within 30 minutes after blood sampling in all patients. All specimens were brought to the laboratory by the collecting physician immediately after blood sampling [1].

2.3 | MEA

As described previously, whole blood impedance aggregometry was performed with the Multiplate analyzer (Roche Diagnostics) [2,17,18].

After dilution (1:2 with 0.9% sodium chloride solution) of hirudin-anticoagulated whole blood and stirring in the test cuvettes for 3 minutes at 37 °C, arachidonic acid (AA; 0.5 mM), adenosine diphosphate (ADP; 6.4 μM), or thrombin receptor–activating peptide (TRAP, a protease-activated receptor-1 agonist; 32 μM; all from Roche Diagnostics) was added, and aggregation was continuously recorded for 6 minutes [19]. The adhesion of activated platelets to the electrodes led to an increase in impedance, which was detected for each sensor unit separately and transformed into aggregation units (AU) that were plotted against time. The AU at 6 minutes were used for all calculations. One AU corresponds to 10 AU × minutes (area under the curve of AU) [17,18].

2.4 | Soluble P-selectin

As previously described, soluble P-selectin (sP-selectin) was measured according to the manufacturer's instructions using an enzyme-linked immunosorbent assay (Human sP-Selectin Immunoassay, R&D Systems) [1,2].

2.5 | Statistical analysis

All continuous variables are expressed as median (IQR). Categorical variables are given as number (percentage). Continuous variables were compared by Mann–Whitney U-test. Chi-squared tests were performed for comparisons of categorical variables. Cumulative incidences were calculated using the Kaplan–Meier method and compared using the log-rank test. All statistical tests were 2-tailed, and a P value of <.05 was required for statistical significance. Statistical analyses and figures were performed with SPSS version 29 (IBM SPSS Inc).

2.6 | Clinical endpoint

The endpoints were bleeding events and pump thrombosis over a period of 24 months following LVAD implantation. Bleeding events were defined as gastrointestinal bleeding or hemorrhagic stroke. Pump thrombosis was defined by the presence of major hemolysis; heart failure not explained by structural heart disease or abnormal pump parameters together with an accompanying intervention or event. This intervention or event was either intravenous treatment (anticoagulation, thrombolytics, or antiplatelet therapy), pump replacement/exchange/deactivation, urgent transplant listing, stroke, transient ischemic attack, or death, as described previously [1]. Data were censored at the time of an adverse event or at the end of the follow-up. Clinical follow-up was performed for all patients at the outpatient department of the Department of Cardiac Surgery at the Medical University of Vienna.

3 | RESULTS

In total, 62 patients were available for final analysis. Median age was 62 years (IQR, 55-70 years), and 56 patients (90.3%) were male. HVAD was implanted in 19 patients (30.6%) and HM3 was implanted in 43 patients (69.4%). Table 1 provides an overview of the baseline characteristics of the studied patient cohort.

3.1 | HRPR and markers of platelet function

In line with a large study showing an association of HRPR with ischemic outcomes in patients undergoing PCI [20], MEA AA of ≥21 AU was defined as HRPR. With use of this cutoff, HRPR was detected in 29 patients (46.8%) of the study cohort. The proportion of patients with HM3 was higher than the proportion of patients with HVAD among patients with HRPR because the majority of patients included in our study received an HM3 device (P = .02; Table 1). However, more importantly, the proportion of patients with HRPR was higher in patients with HVAD than in patients with HM3 (68.4% vs 37.2%; P = .02). Other baseline characteristics did not differ significantly between patients without and with HRPR (Table 1).

Table 2 shows the studied platelet function markers in patients without and with HRPR.

Platelet aggregation in response to AA (26 AU [23-33 AU] vs 15 AU [8-17 AU]; P < .001), ADP (68 AU [50-79 AU] vs 56 AU [32-72 AU]; P = .02), and TRAP (107 AU [84-118 AU] vs 78 AU [46-104 AU]; P = .01) as well as sP-selectin levels (47.9 ng/mL [44.3-56.5 ng/mL] vs 40.6 ng/mL [34.1-46.6 ng/mL]; P < .001), were significantly higher in patients with HRPR (Table 2).

3.2 | Platelet reactivity and clinical outcomes

During a median follow-up period of 523 days (IQR, 313-761), 13 patients (21.0%) experienced an adverse event. Ten patients (16.1%) suffered a bleeding complication, and 3 patients (4.8%) had pump thrombosis. In these specific cases, the endpoint "bleeding event" was met by gastrointestinal bleeding in all patients with bleeding events. The endpoint "pump thrombosis" was met by abnormal pump parameters due to systemic embolization requiring lysis therapy in 1 patient (1.6%) and abnormal pump parameters requiring pump replacement in 2 patients (3.2%). Nine patients (15.3%) died during follow-up (Table 3).

AA-inducible platelet aggregation by MEA was significantly higher in patients with pump thrombosis (28 AU [26-30 AU] vs 20 AU [15-25 AU]; P = .01; Figure 1A), whereas no significant differences were detected for ADP-inducible (53 AU [46-82 AU] vs 60 AU [38-77 AU]; P = >.99) and TRAP-inducible platelet aggregation (95 AU [63-119 AU] vs 97 AU [67-116 AU]; P = >.99). P-selectin levels were comparable between patients without and those with pump thrombosis (44.3 ng/mL [36.4-48.8 ng/mL] vs 46.6 ng/mL [36.5-52.1 ng/mL]; P = .8).

AA-inducible platelet aggregation was similar in patients without and with bleeding events (20 AU [15-25 AU] vs 15 AU [10-31 AU]; P = .9; Figure 1B). Similarly, platelet aggregation in response to ADP and TRAP was comparable between patients without and those with bleeding events (ADP, 64 AU [42-78 AU] vs 55 AU [42-68 AU]; P = .5; TRAP, 99 AU [67-117 AU] vs 83 AU [67-112 AU]; P = .4). P-selectin levels were comparable between patients without and those with a bleeding event (45.1 ng/mL [36.5-51.6 ng/mL] vs 43.9 ng/mL [34.9-46.6 ng/mL]; P = .5).

All pump thromboses occurred in patients with HRPR (3 vs 0; P = .06; Table 3; Figure 2A). The rate of bleeding events was similar in patients without and with HRPR (18.2% vs 13.8%; P = .6; Table 3; Figure 2B). The corresponding Kaplan–Meier analyses revealed no significant differences in the incidence of both pump thrombosis (log-rank P = .07) and bleeding (log-rank P = .7) between patients without and with HRPR throughout the follow-up period (Figure 2A, B).

TABLE 1 Baseline characteristics of patients without vs with high on-treatment residual platelet reactivity.

Characteristics	No HRPR (n = 33)	HRPR (n = 29)	P
Demographics			
Age (y)	64 (56-69)	59 (53-70)	.4
Caucasian, White	33 (100)	29 (100)	
Male patients	29 (87.9)	27 (93.1)	.5
Body mass index (kg/m^2)	29.9 (25.6-31.0)	27.9 (25.8-32.4)	.9
Medical history			
Arterial hypertension	20 (60.6)	14 (48.3)	.3
Hyperlipoproteinemia	18 (54.5)	12 (41.4)	.3
Peripheral artery disease	2 (6.1)	2 (6.9)	.6
Diabetes mellitus type 2	9 (27.3)	6 (20.7)	.6
Smoker	1 (3.0)	1 (3.4)	.5
Prior stroke or TIA	5 (15.2)	3 (10.3)	.1
Prior myocardial infarction	24 (75.0)	20 (69.0)	.6
CAD	24 (72.7)	22 (75.9)	>.99
1-vessel disease	7 (21.2)	7 (24.1)	
2-vessel disease	9 (27.3)	8 (27.6)	
3-vessel disease	8 (24.2)	7 (24.1)	
Cardiomyopathy			.8
Ischemic	25 (75.8)	21 (72.4)	
Dilatative	8 (24.2)	8 (27.6)	
LVAD device			.02
HVAD	6 (18.2)	13 (44.8)	
HM3	27 (81.8)	16 (55.2)	
Laboratory data			
Serum creatinine (mg/dL)	1.58 (1.12-2.02)	1.18 (0.98-1.47)	.1
Platelet count (G/L)	211 (170-256)	241 (186-278)	.3
High sensitivity CRP (mg/dL)	0.37 (0.16-0.61)	0.33 (0.16-0.68)	.7
proBNP (pg/mL)	1238.0 (898.2-2222.5)	1416.0 (665.7-2595.0)	>.99
Medication			
Clopidogrel	2 (6.1)	0	.2
Statin	22 (66.7)	21 (77.8)	.3
Beta-blocker	22 (66.7)	18 (64.3)	.8
ACE inhibitor	20 (60.6)	14 (48.3)	.3
ARB	1 (3.0)	4 (13.8)	.1
Calcium channel blocker	6 (18.8)	2 (6.9)	.2

Continuous data are shown as median (IQR). Dichotomous data are shown as n (%).

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CRP, C-reactive protein; HRPR, high on-treatment residual platelet reactivity; HM3, HeartMate 3; LVAD, left ventricular assist device; proBNP, pro–brain natriuretic peptide; TIA, transient ischemic attack.

3.3 | HRPR and clinical outcomes in HVAD vs HM3

Regarding the implanted LVAD devices, there were no significant differences in bleeding events between HM3 and HVAD during the follow-up period (16.3% vs 15.8%; P = .9). However, all patients with a pump thrombosis were HVAD patients (3 vs 0; P = .01; Table 4), and the corresponding device-specific Kaplan–Meier analysis showed a significantly higher event rate of pump thrombosis in HRPR patients with HVAD than in HVAD patients without HRPR and HM3 patients without and with HRPR (log-rank P = .005; Figure 2C). In accordance with these findings, platelet aggregation in response to AA was significantly lower in HM3 patients than in patients with HVAD (18 AU [13-23 AU] vs 24 AU [17-30 AU]; P = .04; Table 4), whereas ADP- and TRAP-inducible platelet aggregation was comparable between patients with HM3 and HVAD (ADP, 63 AU [42-77 AU] vs 53 AU [38-78 AU]; P = .6; TRAP, 97 AU [67-118 AU] vs 95 AU [63-114 AU]; P = .9). There were no significant differences in the number of deaths between HM3 and HVAD patients during follow-up (14.0% vs 15.8%; P = .8; Table 4).

4 | DISCUSSION

To the best of our knowledge, this is the first study investigating the role of on-treatment platelet reactivity in adverse outcomes in stable LVAD patients receiving antithrombotic therapy with a VKA and low-dose aspirin. AA-inducible platelet aggregation by MEA was significantly higher in patients with pump thrombosis. HRPR was highly prevalent in LVAD patients. Patients with HRPR also showed increased platelet reactivity to ADP and TRAP as well as higher levels of sP-selectin, and all pump thromboses occurred in patients with HRPR.

TABLE 2 Parameters of platelet function in patients with high on-treatment residual platelet reactivity vs patients with adequate response to aspirin.

Parameters	No HRPR (n = 33)	HRPR (n = 29)	P
MEA AA (AU)	15 (8-17)	26 (23-33)	<.001
MEA ADP (AU)	56 (32-72)	68 (50-79)	.02
MEA TRAP (AU)	78 (46-104)	107 (84-118)	.01
Soluble P-selectin (ng/mL)	40.6 (34.12-46.62)	47.89 (44.30-56.53)	<.001

Data are presented as median (IQR).

AA, arachidonic acid; ADP, adenosine diphosphate; AU, aggregation units; HRPR, high on-treatment residual platelet reactivity; MEA, multiple electrode aggregometry; TRAP, thrombin receptor–activating peptide.

TABLE 3 Clinical outcomes.

Event	No HRPR (*n* = 33)	HRPR (*n* = 29)	*P*
AE at 6 mo	4 (12.1)	3 (10.3)	.9
AE at 12 mo	6 (18.2)	3 (10.3)	.3
AE at 24 mo	8 (24.2)	5 (17.2)	.8
Major bleeding at 24 mo	6 (18.2)	4 (13.8)	.6
Pump thrombosis at 24 mo	0	3 (10.3)	.06
Death	5 (15.1)	4 (13.8)	.8

Dichotomous data are shown as *n* (%).

AE, adverse event; HRPR, high on-treatment residual platelet reactivity.

It has been previously reported that HRPR is predictive for thrombotic events and bleeding complications in several cohorts with atherosclerotic cardiovascular disease [11,12,20,21]. Mayer et al. [11,20] studied the association of HRPR with ischemic outcomes in a cohort of patients undergoing PCI on dual antiplatelet therapy (DAPT) with a 1-year follow-up. They found a significantly increased risk of stent thrombosis and cardiovascular death in patients with HRPR [11]. In contrast, Stone et al. [12] reported no association of HRPR with stent thrombosis in CAD patients on DAPT within 1 year after PCI. However, HRPR was inversely linked to bleeding events in their study. In a cohort of patients with peripheral artery disease, Kremers et al. [21] showed that patients who experienced a composite endpoint of myocardial infarction, ischemic stroke, acute limb ischemia, elective PCI, or coronary artery bypass grafting during a follow-up period of 1 year were more likely to have HRPR. However, when interpreting these previous results in comparison with the present study, it has to be considered that (1) the cited studies [11,12,20,21] analyzed larger cohorts, (2) their patients received a different antithrombotic regimen and were not anticoagulated with a VKA, (3) different platelet function tests were used, and (4) HRPR definitions varied from study to study. Mayer et al. [11,20] defined HRPR as MEA AA of ≥191 AU × minutes [11] and MEA AA of ≥203 AU × minutes [20], whereas Stone et al. [12] and Kremers et al. [21] defined HRPR as >550 aspirin reaction units in the VerifyNow aspirin assay (Accumetrics). Given the large cohort size of the second study by Mayer et al. [20], we decided to apply their cutoff value of MEA of ≥203 AU × minutes in our analysis. Since 1 AU corresponds to 10 AU × minutes, MEA AA of ≥21 AU was considered as HRPR in our study.

No reports on the association of on-treatment platelet reactivity with adverse outcomes have been published in LVAD patients so far. Pump thrombosis is a rare but serious complication in LVAD patients [22]. Risk factors for pump thrombosis are inadequate anticoagulation and positioning of the device [3,22]. With regard to the established thrombotic risk of HRPR, data on its prevalence and association with outcomes are of clinical importance as they may allow better risk stratification of LVAD patients. In our analysis, HRPR was highly prevalent among LVAD patients and linked to higher agonist-inducible platelet aggregation by MEA and higher sP-selectin levels. Both HRPR by MEA and high sP-selectin have previously been associated with thrombotic events in cardiovascular disease [23–25]. sP-selectin is known for its proatherosclerotic properties, which encompass the augmentation of leukocyte recruitment and the modulation of thrombotic responses [26]. Tscharre et al. [27] have previously shown a correlation between elevated sP-selectin levels and an increased risk

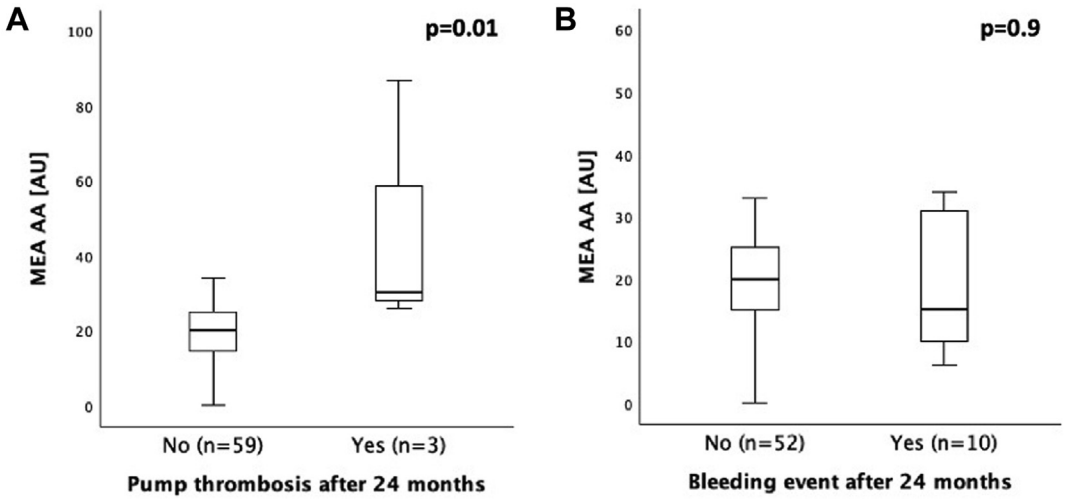

FIGURE 1 Arachidonic acid (AA)–inducible platelet aggregation in aggregation units (AU) by multiple electrode aggregometry (MEA) in (A) patients without and with pump thrombosis and (B) patients without and with bleeding events.

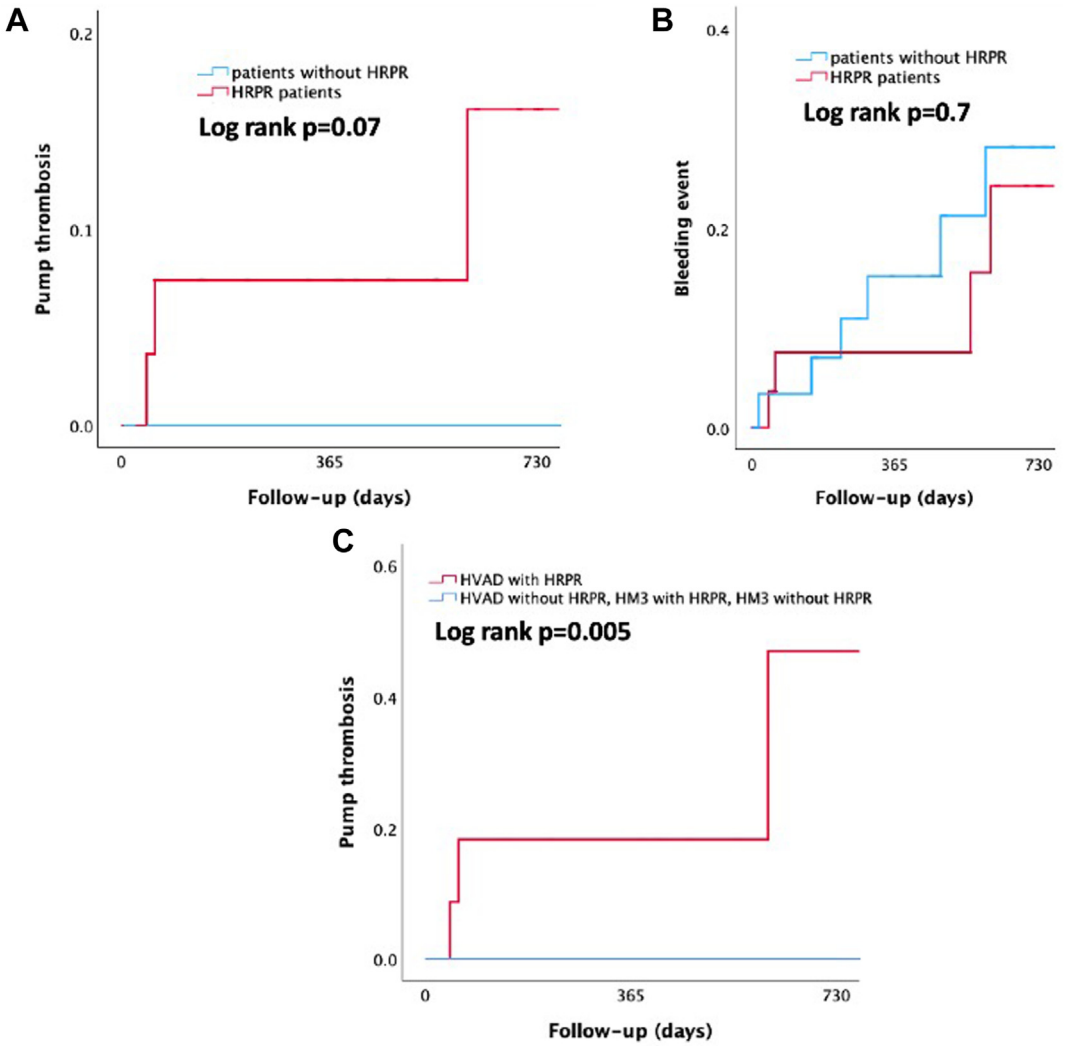

FIGURE 2 Kaplan–Meier curve analysis for (A) pump thrombosis comparing patients without and with high on-treatment residual platelet reactivity (HRPR), (B) bleeding events comparing patients without and with HRPR, and (C) pump thrombosis comparing HVAD patients with HRPR and HVAD patients without HRPR and HeartMate 3 (HM3) patients without and with HRPR.

of long-term major cardiovascular events in CAD patients undergoing PCI. However, in the current study, there were no significant differences in sP-selectin levels between patients without and with pump thrombosis and between those without and with bleeding events. This may be due to the small sample size and the low number of outcome events. Finally, we previously reported comparable levels of sP-selectin in HVAD and HM3 patients [1].

AA-inducible platelet reactivity was significantly higher in LVAD patients with subsequent pump thrombosis in our study. In line with these findings, patients with HRPR had a numerically higher risk of pump thrombosis in the studied cohort. However, due to the small number of patients and pump thromboses, our results have to be interpreted with great caution and should be considered as hypothesis-generating only.

With regard to the implanted LVAD devices, HVAD and HM3, pump thrombosis was only detectable in the HVAD cohort during follow-up. Likewise, on-treatment residual AA-inducible platelet aggregation was significantly higher in HVAD patients than in those with HM3 despite the higher daily aspirin dose in patients with HVAD (200 mg/d in HVAD patients vs 100 mg/d in HM3 patients). Consistent with these findings, recent data show virtual elimination of de novo pump thrombosis in HM3 patients [28]. Moreover, analyses of the MOMENTUM-3 trial suggest that there are no differences in hemocompatibility between patients receiving high-dose (325 mg/d) or low-dose (81 mg/d) aspirin [29]. These results have led to the hypothesis that antiplatelet therapy with aspirin may be omitted in HM3 patients, thereby reducing the risk of bleeding events. Indeed, the ARIES HM3 trial recently investigated the safety and efficacy of an antiplatelet-free antithrombotic regimen in HM3 patients [30]. Thereby, Mehra et al. [30] showed that the avoidance of aspirin reduces the risk of nonsurgical bleeding without increasing the risk of thromboembolism. These data suggest that aspirin can be safely omitted in HM3 patients and raise the question if on-treatment platelet reactivity is only a marker of risk in HVAD patients or

TABLE 4 Clinical outcomes related to the implanted left ventricular assist device.

Clinical outcomes and parameters	HM3 (n = 43)	HVAD (n = 19)	P
Bleeding event	7 (16.3)	3 (15.8)	.9
Pump thrombosis	0	3 (15.8)	.01
Death	6 (14.0)	3 (15.8)	.8
HRPR	16 (36.2)	13 (68.4)	.02
MEA AA (AU)	18 (13-23)	24 (17-30)	.04
MEA ADP (AU)	63 (42-77)	53 (38-78)	.6
MEA TRAP (AU)	97 (67-118)	95 (63-114)	.9
Soluble P-selectin (ng/mL)	45.0 (36.4-48.8)	44.5 (40.7-52.1)	.8

Dichotomous data are shown as n (%). Continuous data are presented as median (IQR).

AA, arachidonic acid; ADP, adenosine diphosphate; AU, aggregation units; HM3, HeartMate 3; HRPR, high on-treatment residual platelet reactivity; MEA, multiple electrode aggregometry; TRAP, thrombin receptor–activating peptide.

potentially a risk marker that is independent of the applied antithrombotic regimen [30]. Since all pump thromboses in our study occurred in HVAD patients with HRPR and the rate of pump thrombosis in patients with HM3 was extremely low in recently published large prospective trials [28–32], one may speculate that HRPR represents a risk marker for pump thrombosis, particularly in HVAD patients. These questions can only be answered by adequately powered clinical trials. Until then, our data on a potential influence of HRPR on pump thrombosis in HVAD patients should be considered hypothesis-generating only due to the low event rate (n = 3) in the studied cohort. Moreover, the device-specific Kaplan–Meier analysis (Figure 2C) indicates that the type of LVAD (HVAD or HM3) might have had a decisive impact on the occurrence of pump thrombosis.

Furthermore, to facilitate a more comprehensive analysis of a potential prothrombotic milieu in HVAD and HM3 patients, exploring additional thromboembolic endpoints in future trials seems advantageous. However, with regard to the endpoint definition "pump thrombosis," no strokes or transient ischemic attacks were detectable in the corresponding endpoint analysis of the present study cohort.

We found no association between bleeding events and HRPR in the present study. These results are in contrast to the findings by Stone et al. [12], who demonstrated an inverse association of HRPR with bleeding events in CAD patients on DAPT within 1 year following PCI. Accordingly, on-treatment platelet reactivity in patients receiving oral anticoagulation with a VKA may play only a minor role in bleeding risk. As the risk of bleeding in LVAD patients remains problematic despite the implementation of newer continuous flow devices, bleeding may also be a consequence of the unnatural circulatory physiology in these patients [29,33].

In summary, on-treatment platelet reactivity is associated with pump thrombosis in LVAD patients. One may therefore speculate that the implementation of platelet function assays as screening tools could help to identify LVAD patients at an increased risk of pump thrombosis in order to include them in a tighter control regimen and/or switch them to an alternative antithrombotic strategy. However, given the small number of patients in the current study, any of these further considerations demand additional data from large prospective clinical trials.

4.1 | Limitations

With regard to the results of the study, the following limitations must be considered. First, this was a monocentric study. Therefore, monocentric bias cannot be excluded. Second, we did not assess if LVADs were implanted as a "bridge to transplant," a "bridge to recovery," or "destination therapy." However, since all included patients received antithrombotic therapy with aspirin and phenprocoumon, the main findings of the study should not be influenced by the primary LVAD indication. Third, patients with HVAD and HM3 were prescribed different doses of aspirin (200 mg/d vs 100 mg/d). However, previous studies have shown complete inhibition of thromboxane synthesis with 75 mg aspirin daily [26]. Moreover, in the present analysis, AA-inducible platelet reactivity was higher and HRPR was more frequent in HVAD patients despite higher aspirin doses in this subgroup. Accordingly, a decisive influence of aspirin dosage on the occurrence of HRPR and outcomes seems unlikely. Fourth, platelet aggregation was only measured at a single time point and may vary over time due to different influencing factors like diet or anxiety/stress. Nevertheless, the results of our study suggest that platelet aggregation should be further investigated as a potential future risk marker in stable LVAD patients that can be easily obtained in daily clinical routine. Finally, we observed an overall low incidence of thromboembolic endpoints, with only 3 cases of pump thrombosis. In addition, the study cohort was rather small. Therefore, the results should be interpreted with great caution and considered as hypothesis-generating only.

5 | CONCLUSION

Platelet reactivity is associated with pump thrombosis in LVAD patients. HRPR may represent a risk marker for pump thrombosis, particularly in HVAD patients. Large prospective clinical trials are needed to further study the clinical impact of HRPR in LVAD patients and evaluate differences between available pump types as well as potential therapeutic strategies.

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AUTHOR CONTRIBUTIONS

Conceptualization: D.M., M.T., and T.G.; methodology: M.T., F.W., D.K., P.P.W., and T.G.; software: D.M.; validation: M.T. and T.G.; formal analysis: D.M. and T.G.; investigation: D.M., M.T., D.K., P.P.W., S.L., and T.S.; resources: B.E., S.P., T.S., G.L., D.W., D.Z., and T.G.; data curation:

M.T., F.W., D.K., P.P.W., S.L., and T.S.; writing—original draft preparation: D.M. and T.G.; writing—review and editing: M.T., T.S., G.L., S.P., D.W., D.Z., and T.G.; visualization: D.M.; supervision: T.G.; project administration: T.G.; funding acquisition: M.T. and T.G. All authors have read and agreed to the published version of the manuscript.

RELATIONSHIP DISCLOSURE

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ORCID

David Mutschlechner https://orcid.org/0000-0002-3189-6204

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