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Case report

Mechanisms of Gastrointestinal Bleeding in LVAD-Supported Patients: A Two-Hit Model of Hemostatic Disruption and Pathologic Angiogenesis

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Abstract Gastrointestinal bleeding is the most frequent adverse event in patients with advanced heart failure supported by a left ventricular assist device (LVAD). In addition to contributing to increased morbidity and mortality, recurrent bleeding often necessitates blood transfusions, which can lead to human leukocyte antigen (HLA) sensitization—thereby narrowing the pool of compatible donor organs and heightening the risk of graft rejection after transplantation. Angiodysplasias are the most common source of gastrointestinal bleeding in this population, yet its underlying mechanisms remain incompletely understood. In this review, we synthesize current knowledge on the pathophysiology of angiodysplasia-related bleeding in LVAD recipients and propose mechanistically informed treatment strategies tailored to individual pathophysiological profiles.

Key words Gastrointestinal, bleeding, Heart Failure, LVAD

Introduction

Despite major advances in pharmacologic and device-based therapies, approximately 12% of patients with heart failure progress to end-stage disease requiring advanced interventions.[1] With the aging population and rising prevalence of obesity, the number of patients reaching end-stage heart failure is projected to double by 2050.[2] Orthotopic heart transplantation remains the gold standard for eligible patients, but its widespread use is limited mainly by donor organ shortages and recipient comorbidities. As a result, waitlist times have lengthened substantially, with 1-year mortality on the transplant list approaching 30% in some centers.[3]

To address this treatment gap, durable mechanical circulatory support—most commonly with left ventricular assist devices (LVADs)—has emerged as a viable alternative. Following the pivotal REMATCH trial, which demonstrated a survival benefit of LVAD therapy over optimal medical management, LVAD implantation rates have risen steadily.4 However, this growth has been paralleled by a rise in LVAD-related complications, most notably gastrointestinal (GI) bleeding, which has become the most frequent long-term adverse event.

Within the first year after implantation, approximately 20% of LVAD recipients experience GI bleeding; this number increases to nearly one-third by the end of the second year.5 Beyond its direct morbidity, major GI bleeding is associated with increased mortality and frequently necessitates transfusions, which can lead to human leukocyte antigen (HLA) sensitization which further reduces patient's transplant eligibility.

Angiodysplasias are the most commonly identified source of GI bleeding in this patient population, accounting for up to 60% of all bleeding episodes.6 Despite their high prevalence, the pathophysiological mechanisms underlying angiodysplasia formation and bleeding in LVAD recipients remain poorly understood, and current prevention and treatment strategies remain suboptimal. In this review, we synthesize current knowledge on the pathogenesis of angiodysplasia-related bleeding in patients receiving continuous-flow LVAD support and propose mechanistically informed treatment strategies tailored to individual pathophysiological profiles.

Acquired von Willebrand disease

Acquired von Willebrand disease (AVWD) is a well-established cause of GI bleeding in conditions associated with high shear stress. This mechanism was first recognized in the context of what became known as Heyde's syndrome, following Edward C. Heyde's observation of increased GI bleeding in patients with severe aortic stenosis.[7] Under high shear conditions, high-molecular-weight (HMW) von Willebrand factor (vWF) multimers undergo a conformational change from a globular to an elongated structure, which exposes their A2 domain—the cleavage site for the metalloprotease ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13).[8,9] Proteolytic cleavage at this site preferentially depletes the largest, most hemostatically active vWF multimers, impairing their ability to mediate platelet adhesion to subendothelial collagen

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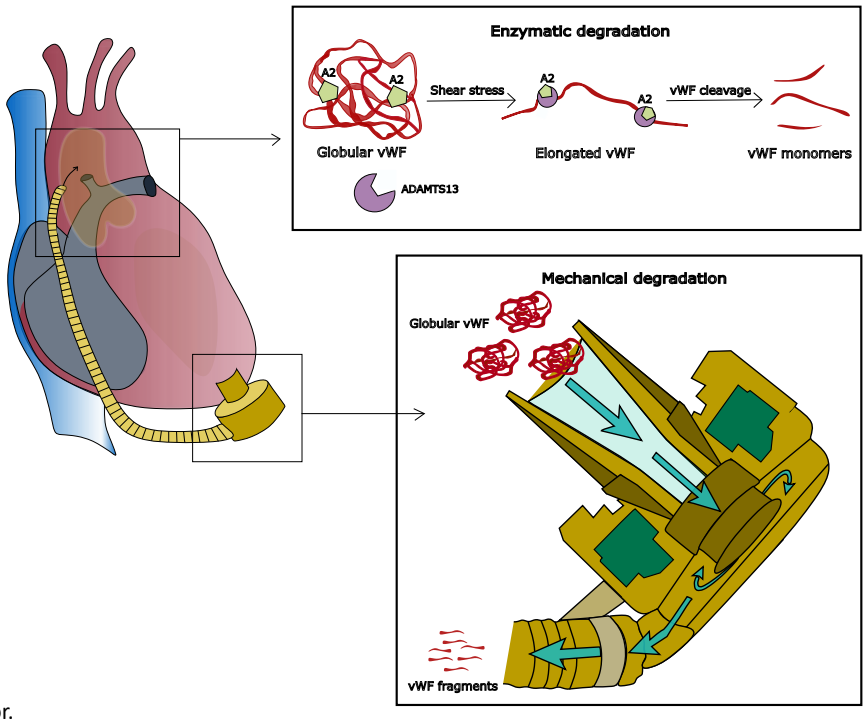
Figure 1. Schematic representation of von Willebrand factor (vWF) degradation in patients supported with a left ventricular assist device (LVAD). Supraphysiological shear stress within the LVAD circulation causes elongation of otherwise globular vWF multimers, thereby exposing cleavage sites for the metalloprotease ADAMTS13, resulting in enzymatic degradation of vWF. Additionally, shear stress and direct contact with the impeller contribute to mechanical fragmentation, further compromising the structural integrity of vWF.



vWF, von Willebrand factor.

and to stabilize circulating coagulation factor VIII. This selective loss impairs both primary and secondary hemostasis, resulting in a bleeding diathesis that most often manifests as mucosal bleeding.[10]

Much like the high shear stress generated across a stenotic aortic valve in Heyde's syndrome, the impeller-driven flow in continuous-flow LVADs exposes blood components to supraphysiological shear forces. These forces can exceed physiological vascular shear stress by more than twofold, far surpassing the shear rates encountered in native arterial circulation thereby creating conditions that promote unfolding of HMW vWF multimers and their subsequent proteolytic cleavage by ADAMTS13.[11,12] To replicate these hemodynamic conditions, various in vitro models have been developed using either high-speed vortexing devices or closed-loop mock circulatory systems simulating LVAD-induced flow.13,14 Across models, exposure of whole blood samples to elevated shear stress consistently resulted in degradation of HMW vWF, with a corresponding increase in low-molecular-weight multimers and proteolytic vWF fragments. Importantly, Bartoli et al. demonstrated that high shear stress can also induce vWF degradation in the absence of ADAMTS13, resulting in a distinct fragmentation pattern.[13] This finding suggests that, in addition to enzymatic proteolysis, non-enzymatic mechanical fragmentation may contribute to the development of AVWD in LVAD-supported patients (Figure 1).

These experimental findings are corroborated by clinical studies demonstrating a near-universal loss of HMW vWF following LVAD implantation, independent of patient characteristics and across different device generations including HeartMate II and HeartMate 3.[13–20] Notably, significant vWF degradation has been observed as early as seven days post-implantation, while restoration of the normal vWF multimer profile has been reported following the first few hours after LVAD explantation due to cardiac recovery or heart transplantation.[21–23] Together, these observations provide compelling evidence for a direct, causative relationship between continuous-flow mechanical circulatory support and AVWD.

The role of vWF structure in gastrointestinal bleeding

Although nearly all LVAD recipients exhibit significant degradation of HMW vWF multimers, only an estimated 18–40% develop GI bleeding.[24] This discrepancy suggests that the mere presence of AVWD may not be sufficient to predict bleeding risk, and that quantitative assessment of its severity may be more informative.

Early studies attempted to correlate GI bleeding with AVWD severity using semiquantitative methods, such as visual grading of multimer distribution on Western blots by expert hematologists. In these systems, band intensity and distribution were scored on a four-point scale (0: no loss of HMW multimers; 3: marked loss). However, these approaches failed to demonstrate a statistically significant association between multimer loss and GI bleeding. Moreover, they were limited by interobserver variability, lack of standardization, and the inherent subjectivity of visual assessment.[15,25,26]

To address these limitations, Mayer et al. applied densitometric analysis to quantify vWF multimer distribu-

tion in 102 patients supported by HVAD or HeartMate II devices.[16] By calculating the relative area under the densitometric curve for low, intermediate, and high molecular weight bands, they derived a large multimer ratio (HMW vWF as a proportion of total vWF). Although this method was analytically more robust, the large multimer ratio still failed to show a significant association with GI bleeding. This may be explained by similar findings in patients with aortic stenosis, where large multimer ratios often overlapped between affected individuals and healthy controls. Such overlap was attributed, in part, to technical variability, including differences in blot exposure time during immunostaining.[27,28]

To overcome these laboratory-related limitations, Sakatsume et al. introduced the vWF large multimer index—a normalized ratio comparing a patient's HMW multimer signal to that of a healthy control run in parallel on the same gel.28 In a cohort of 41 patients on continuous-flow LVAD support (median follow-up: 591 days), the index was significantly lower in those who experienced GI bleeding compared to non-bleeders (25.0 ± 10.3% vs 37.5 ± 17.8%, P = 0.008). Importantly, the groups were well-matched for age, device type, and hematologic parameters, including international normalised ratio (INR). This study provides compelling evidence that quantitative and standardized multimer analysis may identify patients at higher bleeding risk, offering a potential diagnostic refinement in AVWD-related GI bleeding risk stratification.

Bartoli et al. further advanced the understanding of vWF degradation by extending the analysis beyond multimer loss to include vWF fragment accumulation.20 In a study of 35 patients with paired pre- and post-LVAD implantation blood samples, they demonstrated that the reduction in HMW multimers was accompanied by a significant increase in vWF fragments (P < 0.0001). Over a mean follow-up of 22 months, 13 patients (37 %) developed GI bleeding. Interestingly, neither HMW multimer levels (non-bleeders vs. no-angiodysplasia bleeders vs. angiodysplasia bleeders: 91 ± 5 % vs. 88 ± 3 % vs. 89 ± 5 %; P = 0.24) nor low-molecular-weight multimers (136 ± 31 % vs. 143 ± 39 % vs. 144 ± 34 %; P = 0.90) distinguished patients who developed GI bleeding. Similarly, total vWF fragment levels did not differentiate bleeders from non-bleeders. However, in the subgroup of patients with confirmed angiodysplasia-related bleeding, vWF fragment levels were significantly elevated compared to non-bleeders (184 ± 44 % vs. 149 ± 31 %; P = 0.02), while no significant difference was observed between non-bleeders and those with non-angiodysplasia bleeding (149±54 % vs. 149±31 %; P=0.96). These findings suggest that analyses focused exclusively on HMW multimer depletion may overlook key mechanistic information. A more comprehensive assessment—including both multimer loss and vWF fragment accumulation, and the relative balance between them—may better reflect the contribution of AVWD in angiodysplasia-related bleeding.

Taken together, these observations highlight that GI bleeding in LVAD patients is not a uniform entity—much like in non-LVAD populations, it arises from diverse etiologies. Not all bleeding lesions are mediated by AVWD, and the failure to account for lesion subtype may explain the lack of statistical associations in some of the prior studies. Indeed, Bartoli et al. observed a significant association between elevated vWF fragment levels and GI bleeding only in patients with confirmed angiodysplasia, underscoring the lesion-specific nature of this mechanism.20 Furthermore, although Sakatsume et al. did not perform a subgroup analysis based on bleeding etiology, it is reasonable to infer that the statistically significant association between a reduced vWF large multimer index and GI bleeding was primarily driven by angiodysplasia-related cases.28 Of the 12 patients who experienced bleeding, two had confirmed angiodysplasias, and eight had no identifiable source despite upper and lower endoscopy—strongly suggesting occult small bowel angiodysplasia, which is inaccessible to standard endoscopic procedures and often requires capsule endoscopy for detection.

Disruption in angiopoetic signalling

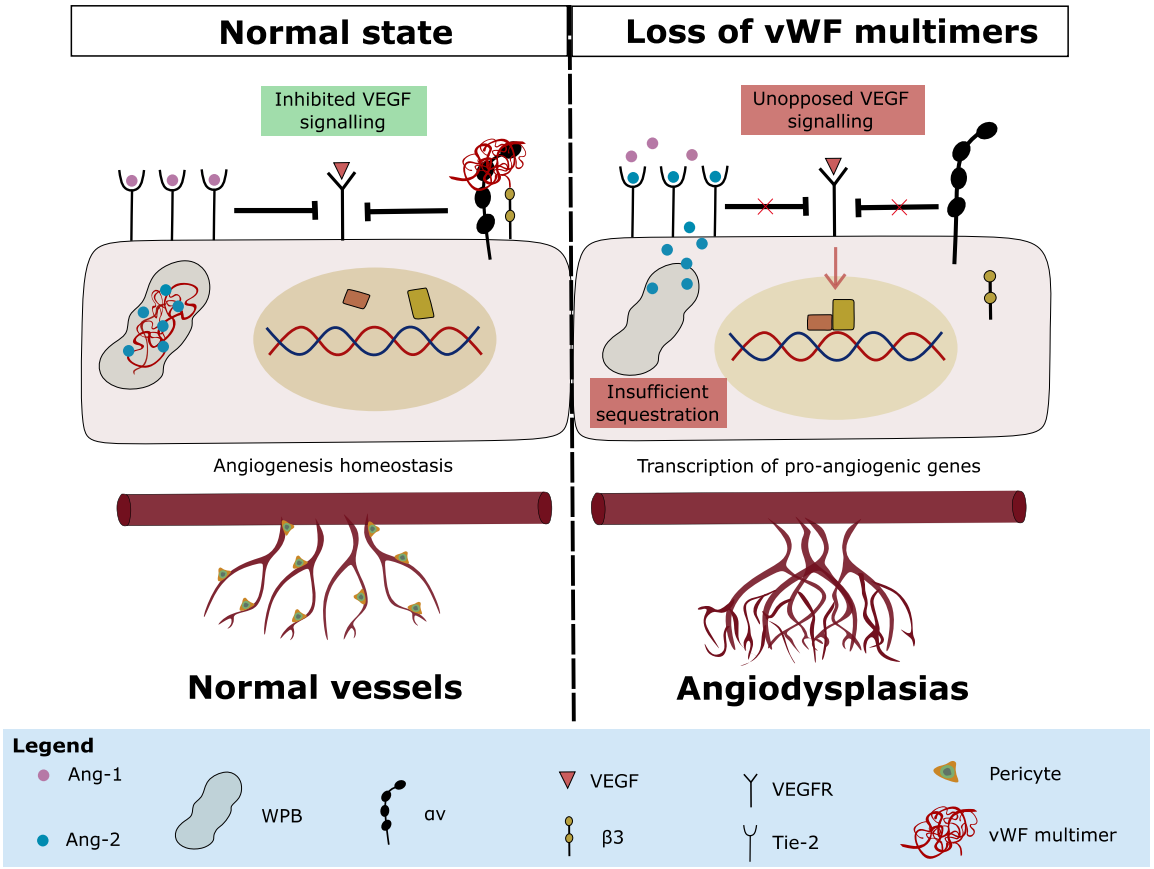
While there is substantial evidence linking structural abnormalities of vWF to an increased risk of GI bleeding in LVAD patients, the role of vWF functional impairment remains less clearly defined and somewhat contradictory.16,28–31 For instance, Sakatsume et al. and Bartoli et al. found no significant association between vWF functional measures and bleeding events, whereas Jahangiri et al. reported the opposite.20,28,30 In their cohort of 74 patients supported by the HeartMate 3 device, both impaired vWF-mediated collagen binding and reduced glycoprotein Ib (GPIb) binding capacity were significantly associated with gastrointestinal bleeding episodes (HR: 2.53; 95% CI: 1.1–5.8; P = 0.02 and HR: 3.7; 95% CI: 1.5–9.2; P = 0.002, respectively).30

These inconsistent findings likely reflect the inclusion of patients with diverse bleeding etiologies. In fact, Jahangiri et al. reported that 33.5% of bleeding episodes were unrelated to angiodysplasia.30 Functional assays—such as collagen binding, platelet aggregation, and factor VIII activity—offer valuable insights into the haemostatic capacity of vWF, but do not capture its broader biological roles.32 As a multimeric glycoprotein, vWF also interacts with and transports a variety of signalling molecules involved in inflammation, wound healing, and angiogenesis.33 This broader functionality may be particularly relevant in angiodysplasia-related bleeding, where impaired regulation of endothelial cell proliferation and migration—not just impaired haemostasis—may be the dominant mechanism. Consequently, traditional functional assays may fail to detect clinically relevant vWF dysfunction in this subset of patients.

Insights into the role of vWF in angiogenesis stem from observations of increased prevalence of angiodysplastic lesions in patients with inherited von Willebrand disease.34 Mechanistically, vWF appears to influence angiogenesis through both extracellular and intracellular pathways, primarily by modulating vascular endothelial growth factor (VEGF) signalling.[35]

Extracellularly, vWF modulates VEGF receptor 2 (VEGFR2) signalling by stabilizing its interaction with integrin

Figure 2. Schematic representation of intracellular and extracellular pathways promoting angiodysplasia formation in the absence of von Willebrand factor (vWF) multimers. Degradation of vWF multimers impairs the intracellular sequestration of angiopoietin-2 (Ang-2) in Weibel-Palade bodies (WPBs), leading to its release and subsequent displacement of angiopoietin-1 from Tie-2 receptors, thereby reducing its inhibitory effect on vascular endothelial growth factor (VEGF) signalling. VEGF signalling is further enhanced by the intracellular translocation of the β3 subunit of the αvβ3 integrin, which in its membrane-bound form normally inhibits VEGF activity. Collectively, due to vWF degradation, VEGF signalling becomes unopposed, promoting the formation of new, immature blood vessels.



vWF, von Willebrand factor; Ang-1, Angiopoietin-1; Ang-2, Angiopoietin-2; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor; WPB, Weibel-Palade bodies.

αvβ3 on the endothelial cell surface. Under physiological conditions, αvβ3 exerts a complex regulatory influence on VEGF signalling, acting as either a promoter or inhibitor of angiogenesis depending on its spatial configuration. The presence of vWF anchors αvβ3 at the membrane and facilitates its association with VEGFR2, thereby attenuating downstream intracellular signalling. In contrast, in the absence of vWF, the β3 subunit undergoes increased internalization and degradation, leading to heightened VEGFR2 sensitivity and unrestrained VEGF-driven endothelial proliferation (Figure 2).[36,37]
Intracellularly, vWF regulates the angiopoietin–Tie2 pathway through its essential role in maintaining the structural integrity and function of Weibel–Palade bodies—specialized endothelial storage granules.38 These organelles store angiopoietin-2 (Ang-2), a context-dependent antagonist of angiopoietin-1 (Ang-1). Under physiological conditions, a tightly regulated balance between Ang-1 and Ang-2 governs Tie2 receptor activation: Ang-1 promotes vascular stability by reinforcing endothelial junctions and recruiting pericytes, whereas Ang-2 competitively inhibits Tie2 signalling, thereby facilitating VEGF-mediated angiogenesis and contributing to the formation of fragile, tortuous vessels.[39] In the absence of vWF, Weibel–Palade bodies lose their capacity to effectively sequester Ang-2, leading to its inappropriate systemic release. Additionally, knockdown of vWF in endothelial cells has been shown to increase Ang-2 transcription, as evidenced by elevated Ang-2 mRNA levels in mice treated with vWF-targeted siRNA (Figure 2).[36]
Despite mounting evidence of disrupted vascular homeostasis in LVAD recipients, the precise molecular drivers of this pathology remain incompletely understood. In vitro studies have shown that endothelial cells exposed to post-LVAD implantation plasma—enriched in vWF fragments—exhibit reduced tubule length and impaired migratory capacity compared to the same patients' pre-implantation plasma, suggesting a shift toward dysfunctional angiogenesis.20 In parallel, Tabit et al. demonstrated that circulating Ang-2 levels are significantly elevated in LVAD patients compared to both heart failure (HF) patients and orthotopic heart transplant (OHT) recipients (LVAD: 12.32 ± 9.57 ng/mL; HF: 5.24 ± 2.98 ng/mL; OHT: 4.39 ± 2.00 ng/mL; P=0.004; LVAD vs. OHT, P=0.004), while VEGF levels were similarly elevated in both HF and LVAD groups.40 Notably,

serum from LVAD patients induced angiogenesis in endothelial cultures in a dose-dependent manner, an effect abolished by Ang-2 neutralizing antibodies—strongly implicating Ang-2 as a key mediator of the observed angiogenic phenotype.

Combining vWF structure and function

Taken together, these findings suggest that vWF degradation not only impairs haemostatic integrity but also disrupts vascular homeostasis, functioning as a "second hit" that simultaneously promotes the formation of new angiodysplasias and heightens the bleeding risk from pre-existing lesions.

Supporting this integrated model, Hennessy-Strahs et al. evaluated a composite bleeding risk score in LVAD-supported patients by combining two parameters: HMW vWF degradation and impaired collagen-binding capacity.41 Individually, structural and functional vWF abnormalities demonstrated only moderate predictive value for all-cause bleeding (PPV: 70 % and 57 %, respectively). However, their combination significantly improved risk stratification, yielding a positive predictive value of 86 %, negative predictive value of 65%, and odds ratio of 11 ($P < .001$). When applied specifically to gastrointestinal bleeding, the model performed even better (PPV: 88 %; NPV: 72 %; OR: 18; $P < .001$).

In addition to validating the multifactorial pathophysiology of bleeding in LVAD recipients, these findings offer mechanistic insights into the etiology of GI bleeding. To determine optimal risk score thresholds, the authors plotted patient-specific changes in vWF function (x-axis) and HMW vWF multimer degradation (y-axis) and identified the linear boundary that best separated bleeders from nonbleeders. Notably, the slope of this line was flatter in the GI bleeding model (–0.05) compared to the all-cause bleeding model (–0.13), indicating a more horizontal orientation.41 This geometric distinction suggests that the GI bleeding risk score was more heavily influenced by vWF structural degradation than by impaired haemostatic function—underscoring the predominant role of vWF fragmentation in the pathogenesis of GI bleeding in LVAD patients.

Hemodynamic Consequences of Continuous-Flow Support

Pivotal trials such as HeartMate II and MOMENTUM-3 established continuous-flow LVADs as the standard of care in advanced heart failure by demonstrating superior durability and improved survival compared to pulsatile systems.42,43 However, despite these advantages, the transition towards continuous-flow support has been accompanied by a marked increase in GI bleeding events. For instance, Crow et al. reported a significantly higher GI bleeding rate among 55 patients with continuous-flow LVADs compared to 46 age- and sex-matched patients on pulsatile support (63 vs. 6.8 events per 100 patient-years; $P = 0.0004$).44 Although the continuous-flow group received both warfarin and aspirin—whereas the pulsatile group received aspirin alone—the modest difference in mean INR (2.0 ± 0.1 vs. 1.6 ± 0.1) and the low variability within the continuous-flow group suggest consistent adherence to the anticoagulation regimen. This makes it unlikely that anticoagulation intensity alone explains the substantially higher bleeding rate. Even more striking was the difference in bleeding source: at least 33% of patients with continuous-flow devices had confirmed angiodysplasias as the source of GI bleeding, whereas no angiodysplasias were reported in the pulsatile group.[44] This evidence points to the loss of physiologic pulsatility as a key contributor to the pathogenesis of GI bleeding in LVAD patients—particularly in the development or unmasking of angiodysplasias.

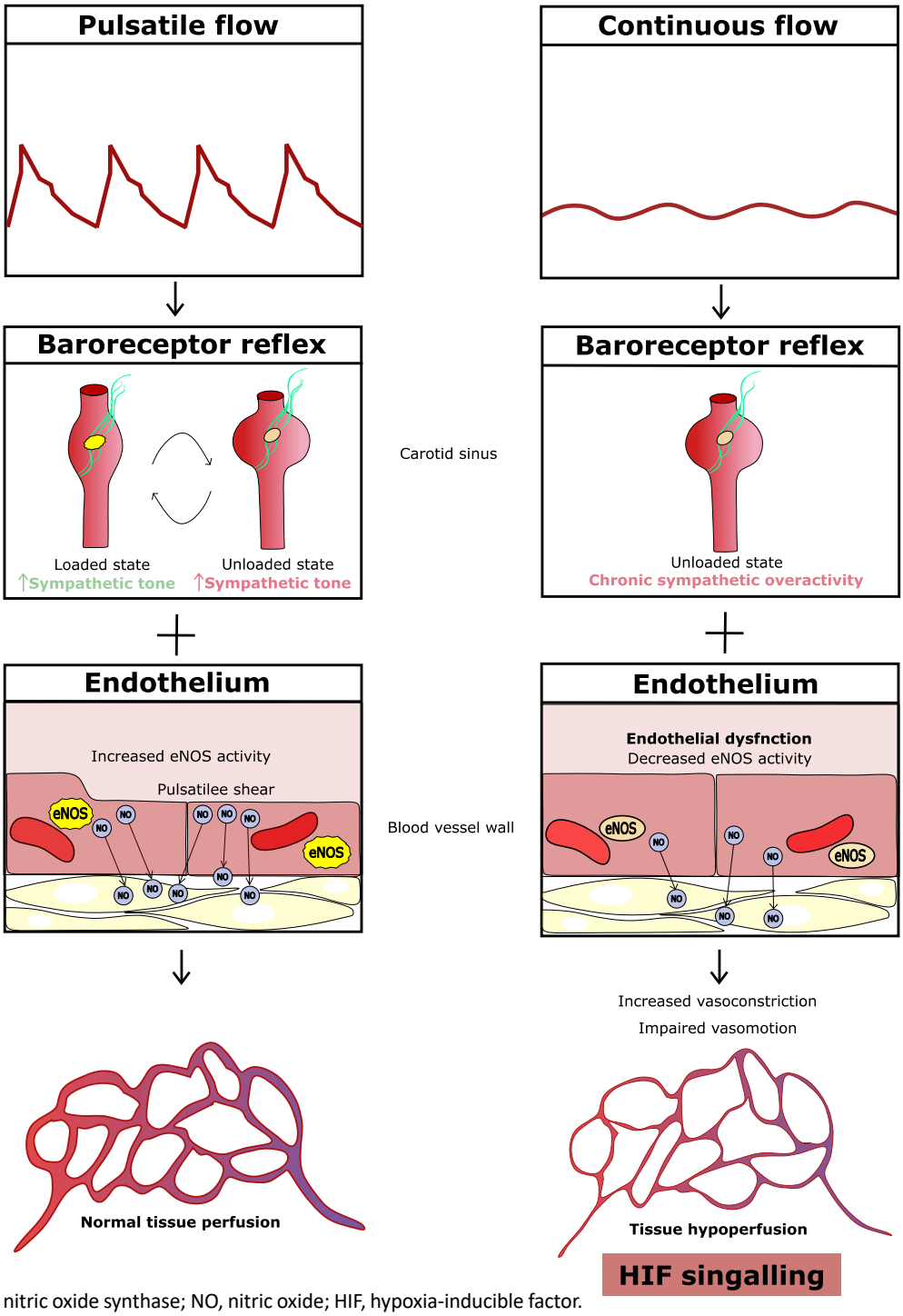
Continuous-flow LVAD support is inherently associated with reduced pulse pressure. By continuously unloading the left ventricle and propelling blood into the aorta, these devices simultaneously lower systolic and raise diastolic arterial pressures—thereby attenuating the normal pulsatile waveform. Under physiological conditions, beat-to-beat fluctuations in arterial pressure activate baroreceptors, eliciting rhythmic sympathetic outflow that drives oscillations in vasomotor tone—crucial for maintaining adequate tissue perfusion.[45] In contrast, diminished pulsatility reduces baroreceptor stimulation, leading to baroreceptor unloading and sustained sympathetic activation. Using microneurography to measure muscle sympathetic nerve activity, Markham et al. demonstrated significantly elevated sympathetic outflow in patients supported by continuous-flow LVADs compared to both pulsatile-flow recipients and healthy controls.[46] Notably, supine sympathetic activity in the continuous-flow group exceeded that of the other groups even in the upright position. This chronic sympathetic overstimulation may promote sustained vasoconstriction, impair dynamic vasomotion, and reduce capillary recruitment—ultimately compromising microvascular oxygen and nutrient delivery.[45,47]

Moreover, under physiological conditions, pulsatile flow exerts rhythmic shear stress on the vascular endothelium—a key stimulus for the activation of endothelial nitric oxide synthase (eNOS) and subsequent nitric oxide (NO) production. In contrast, the continuous flow generated by LVADs leads to reduced mechanotransduction, resulting in diminished NO bioavailability and endothelial dysfunction.48 This is further exacerbated by systemic inflammatory and oxidative stress responses, driven in part by shear-induced activation and foreign surface contact of immune-competent cells, which promote NO degradation and further disrupt microvascular homeostasis.[48,49]

Schematic comparison of pulsatile and continuous flow in relation to gastrointestinal bleeding is presented in Figure 3.

Witman et al. assessed endothelial function by measuring flow-mediated dilation (FMD) of the brachial artery—a validated surrogate of endothelial health—in 22 patients with heart failure with reduced ejection fraction (HFrEF) and 20 patients following continuous-flow LVAD implantation.50 To account for differences in baseline arterial diameter and the shear stimulus generated dur-

Figure 3. Schematic comparison of pulsatile and continuous flow in relation to gastrointestinal bleeding. In the absence of pulsatile shear stress, baroreceptors remain in a chronically unloaded state, resulting in reduced activity of endothelial nitric oxide synthase (eNOS), decreased nitric oxide (NO) production, and increased sympathetic activity. The resulting vasoconstriction and impaired vasomotion contribute to tissue hypoxia, which activates hypoxia-inducible factor (HIF) signalling and promotes angiogenesis.



eNOS, endothelial nitric oxide synthase; NO, nitric oxide; HIF, hypoxia-inducible factor.

ing the test, FMD was normalized to shear rate (%Δ/s^{-1}), providing a more accurate measure of endothelial responsiveness. Patients with continuous-flow LVADs exhibited significantly lower normalized FMD, even when compared to a subgroup of advanced HFrEF patients (NYHA class III/IV) without LVAD support (0.09 ± 0.01 %Δ/s^{-1} vs. 0.13 ± 0.02 %Δ/s^{-1}; $P < 0.05$). Importantly, FMD/shear rate positively correlated with the pulsatility index, implicating reduced pulsatility as a potential driver of endothelial dysfunction in this population.

The combination of diminished availability of vasodilatory mediators and impaired endothelial responsiveness results in a reduced capacity of the peripheral vasculature to appropriately accommodate blood flow in response to metabolic demands, leading to tissue hypoperfusion. This is further exacerbated by sustained vasoconstriction driven by elevated sympathetic tone. Among all vascular beds, the splanchnic circulation is particularly sensitive to autonomic regulation, being particularly sensitive to sympathetic stimulation, making

the gastrointestinal tract especially vulnerable to reductions in perfusion. Chronic submucosal hypoxia inhibits the activity of oxygen-dependent prolyl hydroxylase enzymes, thereby preventing the degradation of hypoxia-inducible factor (HIF). Stabilized HIF accumulates and translocates to the nucleus, where it induces the transcription of proangiogenic genes—most notably VEGF.51 Although direct clinical evidence linking HIF signalling to angiodysplasia formation in LVAD recipients is lacking, indirect support comes from observational data on digoxin. In a retrospective study of 199 continuous-flow LVAD patients, Vukelic et al. found significantly fewer GI bleeding events among those receiving digoxin (16% vs 33%; P = .012).52 Notably, the reduction was specific to angiodysplasia-related bleeding (5% vs 25%; P = .0003), with no significant difference in GI bleeding from other causes—implicating digoxin as an inhibitor of angiogenesis rather than a promoter of haemostasis. Cardiac glycosides such as digoxin have long been recognized in oncology as inhibitors of tumor-driven angiogenesis via suppression of HIF-1α translation.53 The apparent protective effect of digoxin in this setting thus lends indirect support to a role for HIF-mediated signalling in angiodysplasia formation and GI bleeding under conditions of diminished pulsatility.

Finally, pulsatile blood flow plays a crucial role in maintaining vWF homeostasis. Under physiological conditions, shear stress varies with the cardiac cycle—rising during systole to induce partial unfolding of vWF multimers and subsiding during diastole, allowing the molecule to recoil into its globular conformation. In contrast, continuous-flow support generates sustained, unidirectional shear stress that both increases the extent of vWF unfolding and prevents its return to the native conformation. This prolonged exposure of the A2 cleavage domain facilitates persistent ADAMTS13-mediated proteolysis, further disrupting an already imbalanced vWF homeostasis in LVAD patients.[54]

Disruption of thrombocyte function

Platelets are central to effective haemostasis, providing both the initial mechanical barrier to bleeding and a source of procoagulant mediators that stabilize thrombus formation and promote vascular repair. Accordingly, conditions that impair platelet count or function frequently lead to bleeding diatheses. It is therefore unsurprising that platelet dysfunction has emerged as a prominent contributor to bleeding complications in patients supported by mechanical circulatory devices.

Like the vascular endothelium, platelets possess mechanosensitive properties that allow them to respond to hemodynamic stimuli. Under physiological conditions, shear stress plays a key role in platelet activation. In damaged vessels, local vasoconstriction and narrowing accelerate blood flow, exposing platelets tethered to vWF to transient shear forces that unfold vWF multimers and initiate platelet adhesion, activation, and aggregation.55 However, the sustained supraphysiologic shear stress imposed by continuous-flow LVADs disrupts platelet integrity. High shear promotes membrane shedding, releasing platelet-derived microparticles and depleting the platelet surface of critical adhesion and activation receptors.56 In vitro models simulating continuous-flow support have demonstrated reduced expression of GPIbα and GPVI—receptors for vWF and collagen, respectively. These structural alterations translate into functional deficits, evidenced by impaired aggregation responses to ristocetin and collagen.[57]

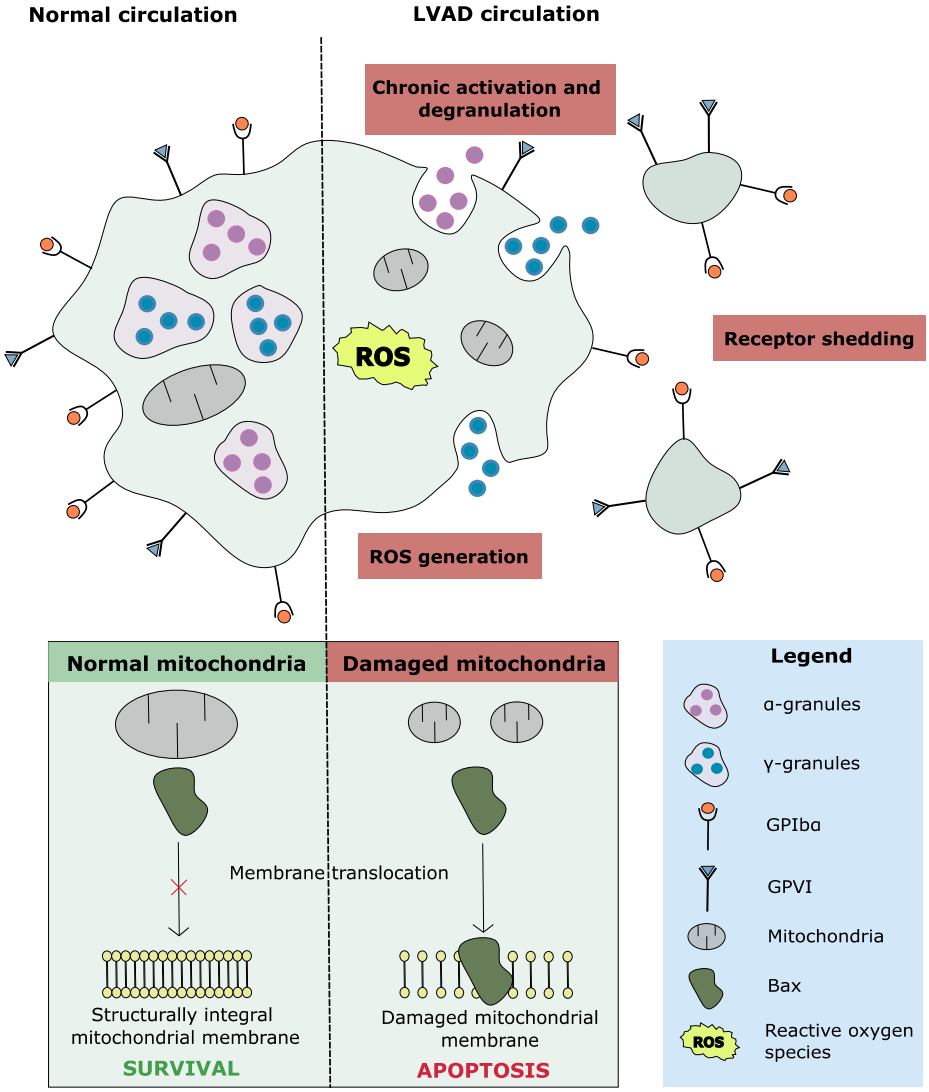
In a prospective analysis of patients undergoing mechanical circulatory support, Mondal et al. demonstrated that reduced platelet surface receptor expression—specifically GPIbα and GPVI—is not exclusive to LVAD support but is already present in advanced heart failure prior to device implantation.[58] However, among the 14 patients who developed nonsurgical bleeding following LVAD placement, the expression of these receptors remained significantly lower at all measured time points compared to non-bleeders. This observation suggests that the degree of shear-induced receptor shedding may be associated with an individual's susceptibility to bleeding, including GI hemorrhage, in the LVAD-supported population.[58]

Further evidence of platelet dysfunction under continuous-flow conditions comes from a study by Liesdek et al., who analyzed paired plasma samples from 32 patients before and after LVAD implantation.59 Mechanical circulatory support was associated with a significant increase in circulating P-selectin levels (144.5 ng/mL vs 115.6 ng/mL; P < .001), a marker of platelet activation. P-selectin is normally stored in α-granules and translocates to the cell surface upon activation, where it promotes leukocyte recruitment and thrombus formation. Its elevation suggests chronic, shear-induced platelet activation. Despite this preactivated state, platelet function was markedly impaired: fibrinogen binding in response to PAR1-activating peptide decreased by 86% post-implantation (P < .001), indicating reduced reactivity.59 Notably, this defect was independent of antiplatelet therapy, as control patients undergoing surgical aortic valve replacement on equivalent regimens exhibited preserved fibrinogen-binding capacity. These findings support a model in which continuous shear exposure and foreign surface contact induce platelet activation, degranulation, and eventual exhaustion— limiting the platelet's ability to respond when haemostasis is critically needed.

Supporting this concept, Klaeske et al. found that LVAD recipients who experienced nonsurgical bleeding had significantly lower platelet responsiveness to ADP compared to non-bleeders (P-selectin$^+$ ADP: 944 vs 1269; P = .04).60 These data reinforce the link between impaired platelet reactivity and bleeding diathesis in the LVAD population.

Beyond mechanical injury, oxidative stress represents an additional mechanism of platelet dysfunction in LVAD recipients. Patients with advanced heart failure already demonstrate elevated oxidative stress due to chronic tissue hypoperfusion and systemic inflammation. LVAD implantation further amplifies this burden through exposure to artificial surfaces and altered flow dynamics, increasing reactive oxygen species (ROS) production and

Figure 4. Schematic comparison of platelet structure and function under normal versus left ventricular assist device (LVAD) hemodynamics. Supraphysiological shear stress induces receptor shedding and chronic platelet activation, thereby impairing their haemostatic function. Moreover, increased reactive oxygen species compromise mitochondrial membrane integrity, permitting the translocation of Bax protein into the membrane and triggering platelet apoptosis.



LVAD, left ventricular assist device; ROS, reactive oxygen species; GPIbα, Glycoprotein Ib alpha subunit; GPVI, Glycoprotein VI.

disrupting redox balance at both systemic and cellular levels.[61,62] ROS impair platelet function by oxidizing receptor domains essential for ligand binding and by promoting receptor shedding.[63] Subsequent analyses revealed a correlation between elevated oxidative stress and increased receptor shedding from platelets, providing a mechanistic explanation for this observation.63 Moreover, oxidative injury to mitochondrial membranes enhances Bax translocation and triggers intrinsic apoptotic pathways, reducing platelet viability. Elevated markers of oxidative stress and mitochondrial-mediated apoptosis have been independently associated with bleeding events in the LVAD population.[63,64]

The impact of LVAD-associated blood flow on platelet structure and function is summarized in Figure 4.

Multiple pathophysiological mechanisms thus contribute to platelet dysfunction under continuous-flow conditions, compromising hemostasis and increasing bleeding risk irrespective of anatomical site. Although no studies to date have directly linked platelet dysfunction to gastrointestinal bleeding in LVAD recipients, the well-established role of platelets in tumor angiogenesis raises the possibility of their involvement in angiodysplasia-related hemorrhage.65 Platelets serve as reservoirs of both pro- and antiangiogenic factors, and tightly regulate vascular remodeling through the controlled release of these mediators from their granules. Disruption of this balance—whether through chronic shear stress, oxidative injury, or premature activation—may favour pathologic angiogenesis, contributing to the formation or expansion of angiodysplasias. Further research is needed to elucidate the role of platelet-derived signalling in GI angiogenesis under conditions of non-physiologic flow, as this could reveal novel therapeutic targets for bleeding prevention in this vulnerable population.

Synthesis of Current Evidence and Potential Treatment Targets

GI bleeding in advanced heart failure patients supported with long-term mechanical circulatory devices is, at least in part, a consequence of device-induced alterations in haemostatic mechanisms. Chief among these are structural and functional changes in vWF and platelets, which compromise both primary and secondary haemostasis. Excessive fragmentation of HMW vWF multimers, the most haemostatically active form, is a hallmark of LVAD-related coagulopathy. Restoration of vWF integrity has therefore emerged as a potential therapeutic goal.

Strategies to increase circulating vWF multimers include infusion of vWF-containing concentrates or pharmacologic mobilization from endothelial storage using desmopressin. While both approaches are well established in the management of hemophilia and type 1 von Willebrand disease, their application in LVAD patients is limited. Desmopressin, for instance, has shown anecdotal benefit in controlling refractory GI bleeding, but its propensity to induce fluid and sodium retention may exacerbate right ventricular dysfunction—a critical concern in this population.[66] Moreover, both infused and endogenously mobilized vWF multimers are rapidly degraded under the persistent high-shear conditions of LVAD support, making these interventions suitable primarily as rescue therapies rather than preventive strategies.

A more durable approach involves inhibition of vWF degradation. Since cleavage by ADAMTS13 is the principal mechanism of vWF fragmentation in LVAD recipients, targeting this metalloprotease offers a mechanistically sound intervention. In vitro studies have shown that doxycycline, a zinc-chelating antibiotic, can inhibit ADAMTS13 activity and preserve vWF multimer integrity.[67] Supporting this, Bartoli et al. demonstrated that doxycycline exposure in an LVAD-simulating flow model increased HMW vWF multimers and reduced vWF fragment formation.68 Similarly, monoclonal antibodies directed at either the catalytic site of ADAMTS13 or the A2 domain of vWF have been shown to attenuate shear-induced vWF fragmentation.[69,70]

However, these strategies are constrained not only by the absence of clinical trial data but also by their potential to induce prothrombotic states. Rapid elevation of circulating multimeric vWF following administration of vWF concentrates or desmopressin may disrupt haemostatic balance, shifting patients from a bleeding diathesis toward thrombosis. Inhibiting ADAMTS13—a key regulatory enzyme of haemostasis—poses an even greater risk, potentially predisposing to thrombotic thrombocytopenic purpura (TTP). While animal studies and observations in individuals with congenital or acquired ADAMTS13 deficiency suggest that inhibition alone may be insufficient to trigger overt TTP, the high prevalence of driveline infections in LVAD recipients could act as a "second hit", further increasing this risk. These considerations underscore the need for caution in applying such therapies in this vulnerable population.

In parallel with vWF degradation, platelet dysfunction is another central contributor to GI bleeding in this population. Continuous shear and oxidative stress lead to platelet receptor shedding, particularly of GPIbα and GPVI, undermining platelet adhesion and activation. These alterations correlate with bleeding events and suggest therapeutic strategies aimed at preserving platelet structure and function. Antioxidant supplementation with agents such as N-acetylcysteine or vitamins C and E represents a feasible, low-risk intervention. Additionally, experimental monoclonal antibodies designed to stabilize GPIbα in the platelet membrane without impairing its function offer a promising, targeted approach that warrants evaluation in LVAD-supported patients.[71]

Angiodysplasia, the leading cause of GI bleeding in LVAD recipients, is likely driven by dysregulated angiogenesis secondary to altered vWF metabolism and chronic submucosal hypoxia. The loss of HMW vWF multimers—along with accumulation of proteolytic fragments—disrupts VEGF signalling, tipping the balance toward aberrant vascular proliferation. This proangiogenic shift is further amplified by reduced pulsatility, which impairs mucosal perfusion and activates HIF signalling. Together, these processes promote the development of fragile, structurally abnormal vasculature, as evidenced by increased submucosal vascular density in jejunal histologic specimens from LVAD-supported animals and humans compared with non-LVAD controls.[72]

Importantly, increased angiogenesis is not unique to LVAD support but is also a well-recognized feature of aging and chronic heart failure.[73] Video capsule endoscopy studies have demonstrated a significantly higher prevalence of GI angiodysplasias in patients with heart failure and reduced ejection fraction compared to age- and comorbidity-matched controls, suggesting that heart failure itself fosters a proangiogenic milieu.[74] Given that chronic hypoperfusion and sustained neurohormonal activation are key pathophysiologic drivers of heart failure progression, it is plausible that optimizing guideline-directed medical therapy (GDMT) may mitigate angiodysplasia formation and thereby reduce gastrointestinal bleeding risk following LVAD implantation. Supporting this hypothesis, retrospective studies have shown that use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is associated with a reduced incidence of GI bleeding in LVAD-supported patients.[75] However, data regarding other components of GDMT remain limited and largely circumstantial.

Targeting dysregulated angiogenic signalling—particularly the VEGF and angiopoietin pathways—offers a promising therapeutic strategy for mitigating GI bleeding in LVAD recipients. Thalidomide, an immunomodulatory agent with indirect anti-VEGF properties, has been shown to significantly reduce bleeding events in this population.[76] However, its clinical use is limited by a high incidence of adverse effects, including peripheral neuropathy, thromboembolic events, and seizures. In contrast, monoclonal antibodies targeting VEGF offer a more selective approach with an improved safety profile. Bevacizumab, a VEGF inhibitor, has demonstrated meaningful reductions in GI bleeding–related hospitalizations, transfusion requirements, and endoscopic interventions in LVAD-supported patients.[77]

Table 1. Summary of the pathological mediators of increased GI bleeding risk in the LVAD population and potential therapeutic strategies addressing them.

von Willebrand factor degradation	
Shear induced vWF fragmentation	vWF concentrates – replenishment of vWF
	Desmopressin – mobilization of intracellularly stored vWF
	Doxycycline – inhibition of metalloproteinase ADAMTS13 by zinc chelation
	Monoclonal antibodies – inhibition of ADAMTS13 or blockade of its interaction with vWF
Platelet dysfunction	
Platelet receptor shedding	Monoclonal antibodies – stabilization of platelet membrane receptors
	Antioxidants – restoration of platelet redox balance
Disrupted angiogenesis	
Formation of structurally immature vessels – angiodysplasias	Optimisation of GDMT – reduction of neurohumoral activation
	Thalidomide and bevacizumab – inhibition of VEGF signalling
	Anti-angipoetin-2 antibodies – restoration of Ang-1/Ang-2 balance
	Digoxin and specific HIF inhibitors – inhibition of HIF signalling
Continuous flow	
Loss of pulsatility	Refined device algorithms – reintroduction of pulsatilty

vWF, von Willebrand factor; GDMT, guideline directed medical therapy; VEGF, Vascular endothelial growth factor; Ang-1, Angiopoietin-1; Ang-2, Angiopoietin-2.

The angiopoietin-Tie2 axis represents an additional target of interest. Preclinical studies have shown that antibodies directed against angiopoietin-2 can inhibit angiogenesis in cultured endothelial cells.40 In addition to reducing vascular density, anti–angiopoietin-2 therapy also increased pericyte coverage of existing vessels, suggesting a role in stabilizing fragile arteriovenous malformations and further lowering the risk of GI bleeding in this high-risk population.[78]

Beyond VEGF signalling, HIF pathways may also contribute to angiogenesis in LVAD recipients. Observational data suggest that digoxin, a known HIF inhibitor, may reduce gastrointestinal bleeding in this population. However, findings have been inconsistent, potentially due to suboptimal HIF inhibition or variability in patient-specific factors.[79] Given HIF's central role in tumor angiogenesis and vascular remodeling, the oncology field has developed several potent and selective HIF inhibitors.[80] These agents may hold therapeutic potential in mitigating pathologic angiogenesis and bleeding risk in LVAD-supported patients, but their role remains to be systematically evaluated in this context.

Engineering advances in LVAD design offer additional opportunities to mitigate GI bleeding. The introduction of the HeartMate 3 device marked a major step forward, replacing the axial-flow design of the HeartMate II with a fully magnetically levitated centrifugal pump. This transition significantly reduced intradevice shear stress, which in turn limited vWF degradation, platelet activation, and receptor shedding—mechanisms implicated in bleeding pathophysiology.81 These hemodynamic improvements translated into clinically meaningful outcomes, with multiple studies demonstrating a lower incidence of GI bleeding in HeartMate 3 recipients compared to earlier-generation devices.[43]

Another innovation incorporated into HeartMate 3 is the introduction of artificial pulsatility through programmed, transient changes in rotor speed (−2000 rpm for 150 ms followed by +2000 rpm for 200 ms). While this algorithm creates fluctuations in flow, the resulting pulse is asynchronous with the native cardiac cycle and differs markedly from physiologic pulsatility.82 In fact, detailed hemodynamic analyses by Stöhr et al. revealed that these speed modulations reduce diastolic flow velocity without producing a corresponding systolic augmentation—effectively generating a "reversed" pulse pattern.[83] Whether this nonphysiologic pulse profile restores microvascular dynamics or improves tissue perfusion remains unclear. Nonetheless, it is conceptually appealing to further refine device algorithms to more closely mimic native pulsatile hemodynamics, which may yield additional reductions in microcirculatory dysfunction and GI bleeding.

Table 1 summarizes the pathological mediators of increased GI bleeding risk in the LVAD population and presents potential therapeutic strategies to address them.

Conclusion

Gastrointestinal bleeding remains one of the most frequent and debilitating complications in patients supported by durable mechanical circulatory devices. It adversely affects quality of life, increases mortality risk, and compromises transplant eligibility through repeated transfusions and HLA sensitization. The pathogenesis reflects a "two-hit" mechanism: on one hand, LVAD-induced hemodynamic alterations disrupt primary haemostatic function—via platelet dysfunction and von Willebrand factor degradation; on the other, these changes promote pathological angiogenesis, leading to the development of structurally immature and fragile vasculature. Although individual bleeding episodes may appear clinically similar, their underlying mechanisms are heterogeneous and often multifactorial. This com-

plexity underscores the need for a systematic, physiology-informed diagnostic and therapeutic approach. Aligning management strategies with the dominant pathophysiologic drivers—whether shear-mediated haemostatic impairment, oxidative injury, or dysregulated angiogenesis—offers the best opportunity to reduce bleeding burden and improve long-term outcomes in this high-risk population.

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