ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2365–2367
Published online 10 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13393

EDITORIAL

Phosphodiesterase type 5 inhibitors after left ventricular assist device: no free lunch?

E. Wilson Grandin[1] and Jeffrey J. Teuteberg[2]

[1]*Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; and* [2]*Cardiovascular Medicine, Stanford University, Stanford, CA, USA*

Even with improvements in device technology, patient selection, implant techniques, and post-operative management, right heart failure (RHF) remains common in patients receiving continuous flow left ventricular assist devices (cf-LVADs). RHF after cf-LVAD is associated with worse survival, renal and hepatic dysfunction, impaired nutrition, longer lengths of stay, and diminished quality of life and functional status.[1] In the USA, driven in part by the recent changes to the heart allocation system, more patients are receiving LVAD as destination therapy (DT), where mitigation of RHF is critical as transplant is not a bailout option.[2]

While multiple factors may impact the development of RHF, increased RV afterload is common and may persist for months despite the reduction in left-sided filling pressures with chronic mechanical unloading. Given the afterload sensitivity of the RV, clinicians treating patients with cf-LVADs have utilized agents developed for the treatment of pulmonary arterial hypertension, particularly phosphodiesterase-5 inhibitors (PDE5is). A recent analysis of the Society for Thoracic Surgery (STS)/Intermacs database highlights that PDE5i use is common in the cf-LVAD population.[3] Preoperatively, PDE5i was utilized in about 10% of patients, and post-operatively, approximately one in three patients were on PDE5i therapy. While the use of PDE5i to ameliorate pulmonary hypertension, and thus RHF, after cf-LVAD is appealing, there is no robust evidence to support its efficacy in this clinical context. Further, uncertainty exists about which patients are mostly likely to benefit, and the optimal timing, dosing, and duration of therapy have not been established. Moreover, there are minimal data on the long-term risks of PDE5i in cf-LVAD patients.

The study by Jackstaite *et al*. in this issue of *ESC Heart Failure* tries to address the question of long-term adverse events with PDE5i therapy after cf-LVAD. Comparing 75 cf-LVAD patients who received PDE5i with 34 patients who did not, the authors assessed the incidence and types of bleeding, RHF, and survival over the first 12 months of support. PDE5i was initiated at the discretion of the treating physician due to early post-operative RHF and was continued to lower persistently elevated pulmonary arterial pressures, reduce pulmonary vascular resistance to enable heart transplantation, or prevent recurrent RHF. Bleeding events occurring after the implant discharge were categorized according to Bleeding Academic Research Consortium (BARC) definitions.

All patients receiving PDE5i were treated for at least 12 months, and 91% received tadalafil with the majority (74%) given 40 mg daily. Overall bleeding events were significantly higher in patients treated with PDE5i as were bleeding events per patient. Surprisingly, those not on PDE5i therapy did not receive a single transfusion for bleeding. The groups had similar use of antiplatelet therapy, and there were no differences in international normalized ratio (INR) values or in the incidence of bleeding attributed to a high INR. The bleeding events were predominantly BARC Type 2, defined as requiring hospitalization for further evaluation or medical, but not surgical, intervention. There were no significant differences in major bleeding or gastrointestinal bleeding. At 1 year, there was no difference in all-cause death or the composite of all-cause death or bleeding. Finally, the incidence of late RHF was similar between groups.

This was a reasonably large group of patients followed for 1 year with details on the type and dosing of PDE5i. Bleeding was well characterized by use of standardized BARC classifications, and transfusion requirements were quantified. Further, the authors documented the intensity and type of anticoagulation and antiplatelet therapy, providing some reassurance that differences in bleeding complications were not related to disparities in the concomitant anti-thrombotic therapy.

One difficulty in contextualizing the results of this study were the substantial baseline differences in the populations. Notably, the PDE5i patients were more likely to be STS/Intermacs Profiles 1 and 2, had a higher frequency of prior bleeding, and, not surprisingly, had a higher incidence of post-implant RHF. The analysis did not include propensity matching, as nearly 70% were on a PDE5i, or a multivariable adjustment for the differences in baseline characteristics.

Therefore, there is uncertainty about whether PDE5i use truly had an independent association with bleeding risk in this cohort. Post-implant haemodynamics were not reported, preventing an assessment of the hemodynamic impact of PDE5i or how haemodynamic profiles might influence bleeding risk. The use of concomitant medications that may impact the incidence of bleeding in cf-LVAD patients, such as angiotensin receptor blockers, was not described. While late RHF was assessed and defined as the development of relevant symptoms requiring readmission, the severity was not characterized using the current STS/Intermacs or recently proposed Academic Research Consortium definitions of late RHF.[4]

When considering the results of this study, we must ask if there is any biological basis for PDE5i to contribute to the risk of bleeding. Prior studies suggest that PDE5i could inhibit platelet function through down-regulation of intracellular pathways. Inhibition of PDE5 results in increased levels of cyclic guanosine monophosphate (cGMP), a second messenger operating through a series of signalling cascades to produce different physiologic effects according to the tissue distribution of PDE5. In vascular smooth muscle cells, cGMP stimulates vasorelaxation, particularly in the pulmonary vascular bed, resulting in decreased resistance to pulmonary blood flow. PDE5 is also abundant in platelets[5] where increased cGMP levels act predominantly via protein kinase G and reduced calcium release from the sarcoplasmic reticulum to blunt platelet activation and adhesion. The administration of the PDE5i sildenafil to healthy volunteers resulted in prolonged bleeding times and decreased *ex vivo* platelet aggregation as induced by collagen.[6] In patients with coronary artery disease, sildenafil similarly blunted platelet activation as evidenced by decreased surface expression of glycoprotein IIb/IIIa receptors.[7] Notably, some studies have suggested that sildenafil may only have a substantial anti-platelet effect at high doses (e.g. 100 mg)[6] or when administered alongside a nitric oxide donor (e.g. sodium nitroprusside).[8,9]

In addition to these plausible biological mechanisms for an antiplatelet effect, a series of published studies support a clinically relevant anti-thrombotic effect of PDE5i. Single-centre studies from Saeed *et al*. and Zayat *et al*. have shown that among patients with a HeartMate2 (Abbott) LVAD and low-level haemolysis, those receiving PDE5i had significantly lower rates of subsequent thromboembolic events, including pump thrombosis and ischaemic stroke.[10,11] These findings were recently corroborated in a large STS/Intermacs analysis of more than 13 000 cf-LVAD patients where the use of PDE5i at any time after implantation was associated with a lower risk of pump thrombosis and ischaemic stroke.[12] Those findings were similar in patients with the axial-flow HeartMate2 and centrifugal-flow HVAD (Medtronic) devices. Importantly, that study also demonstrated a significantly increased risk of gastrointestinal bleeding with PDE5i. Other recent STS/Intermacs analyses have linked both pre-implant[3] and post-implant (Grandin personal communication, manuscript under review) PDE5i use with a higher risk of major bleeding complications after LVAD. Taken together with the current single-centre analysis from Jakstaite *et al*., the evidence increasingly suggests a modest but clinically meaningful anti-thrombotic effect of PDE5i therapy.

The magnitude and impact of an anti-thrombotic effect with PDE5i may vary considerably based on dose, concomitant medications, and other clinical factors that can influence the overall tendency towards thrombosis or bleeding, such as the presence of gastrointestinal arteriovenous malformations. For example, haemolysis liberates plasma free haemoglobin, which can subsequently scavenge nitric oxide, ultimately leading to enhanced platelet activation.[13] In that setting, PDE5i could help restore a more normal balance of cGMP signalling and blunt excess platelet activity.

In the absence of robust data from a randomized clinical trial of PDE5i in LVAD recipients, clinicians must weigh the potential benefits and risks associated with this therapy for each patient. For LVAD recipients with substantial persistent pulmonary hypertension and associated post-implant RHF or potentially with chronic low-level haemolysis, there may be a role for PDE5i. In these higher-risk patients, the potential benefits likely outweigh higher rates of bleeding, particularly if the increased risk is predominantly less severe BARC Type 2 bleeding events. However, in patients with mild RHF, RHF not attributable to increased afterload, a significant history of bleeding, or newer generation devices (HeartMate3, Abbott) with lower risks of both bleeding and pump thrombosis, the risk of PDE5i may outweigh the potential benefits. Although the field of mechanical support has much to learn about the management of chronic RHF and the role of PDE5i therapy for RHF, the results from Jakstaite *et al*. shed some much needed light on the potential risks of PDE5i with cf-LVADs. The information to date on PDE5i should give clinicians pause when initiating PDE5i or at least prompt reassessment of its use in the face of recurrent bleeding events. Even in those high-risk patients treated with PDE5i for significant residual pulmonary hypertension and/or RHF, it may be prudent to perform intermittent haemodynamic surveillance to determine the ongoing need for treatment. While we await more data on the efficacy of PDE5i after cf-LVAD, the findings by Jakstaite *et al*. emphasize the need to better characterize the risks of therapy. Unfortunately, with PDE5i use after cf-LVAD, there is no such thing as a free lunch.

Conflict of interest

E.W.G. declares no conflict of interest. J.J.T. receives advisory board fees from Abiomed, Abbott, Medtronic, and CareDx, serves on the clinical events committee for Abbott, and receives speaking fees from Medtronic, CareDx, and Paragonix.

DOI: 10.1002/ehf2.13393

References

1. Lampert BC, Teuteberg JJ. Right ventricular failure after left ventricular assist devices. *J Heart Lung Transplant* 2015; **34**: 1123–1130.
2. Teuteberg JJ, Cleveland JC Jr, Cowger J, Higgins RS, Goldstein DJ, Keebler M, Kirklin JK, Myers SL, Salerno CT, Stehlik J, Fernandez F, Badhwar V, Pagani FD, Atluri P. The Society of Thoracic Surgeons Intermacs 2019 annual report: the changing landscape of devices and indications. *Ann Thorac Surg* 2020; **109**: 649–660.
3. Gulati G, Grandin EW, Kennedy K, Cabezas F, DeNofrio D, Kociol R, Rame JE, Pagani FD, Kirklin JK, Kormos RL, Teuteberg J, Kiernan M. Preimplant phosphodiesterase-5 inhibitor use is associated with higher rates of severe early right heart failure after left ventricular assist device implantation. *Circ Heart Fail* 2019; **12**: e005537.
4. Kormos RL, Antonides CFJ, Goldstein DJ, Cowger JA, Starling RC, Kirklin JK, Rame JE, Rosenthal D, Mooney ML, Caliskan K, Messe SR, Teuteberg JJ, Mohacsi P, Slaughter MS, Potapov EV, Rao V, Schima H, Stehlik J, Joseph S, Koenig SC, Pagani FD. Updated definitions of adverse events for trials and registries of mechanical circulatory support: a consensus statement of the mechanical circulatory support academic research consortium. *J Heart Lung Transplant* 2020; **39**: 735–750.
5. Hamet P, Coquil J, Bousseau-Lafortune S, Franks D, Tremblay J. Cyclic GMP binding and phosphodiesterase: implication for platelet function. *Adv Cyclic Nucleotide Protein Phosphorylation Res* 1984; **16**: 119–136.
6. Berkels R, Klotz T, Sticht G, Englemann U, Klaus W. Modulation of human platelet aggregation by the phosphodiesterase type 5 inhibitor sildenafil. *J Cardiovasc Pharmacol* 2001; **37**: 413–421.
7. Halcox JP, Nour KR, Zalos G, Mincemoyer R, Waclawiw MA, Rivera CE, Willie G, Ellahham S, Quyyumi AA. The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. *J Am Coll Cardiol* 2002; **40**: 1232–1240.
8. Wallis RM, Corbin JD, Francis SH, Ellis P. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carnae and aortic rings in vitro. *Am J Cardiol* 1999; **83**: 3C–12C.
9. Gudmundsdottir IJ, McRobbie SJ, Robinson SD, Newby DE, Megson IL. Sildenafil potentiates nitric oxide mediated inhibition of human platelet aggregation. *Biochem Biophys Res Commun* 2005; **337**: 382–385.
10. Zayat R, Ahmad U, Stoppe C, Khattab MA, Arab F, Moza A, Tewarie L, Goetzenich A, Autschbach R, Schnoering H. Sildenafil reduces the risk of thromboembolic events in HeartMate II patients with low-level hemolysis and significantly improves the pulmonary circulation. *Int Heart J* 2018; **59**: 1227–1236.
11. Saeed O, Rangasamy S, Selevany I, Madan S, Fertel J, Eisenberg R, Aljoudi M, Patel SR, Shin J, Sims DB, Gil MR, Goldstein DJ, Slepian MJ, Billett HH, Jorde UP. Sildenafil is associated with reduced device thrombosis and ischemic stroke despite low-level hemolysis on Heart Mate II support. *Circ Heart Fail* 2017; **10**: e004222.
12. Xanthopoulos A, Tryposkiadis K, Triposkiadis F, Fukamachi K, Soltesz EG, Young JB, Wolski K, Blackstone EH, Starling RC. Postimplant phosphodiesterase type 5 inhibitors use is associated with lower rates of thrombotic events after left ventricular assist device implantation. *J Am Heart Assoc* 2020; **9**: e015897.
13. Helms C, Marvel M, Zhao W, Stahle M, Vest R, Kato GJ, Lee JS, Christ G, Gladwin MT, Hantgan RR, Kim-Shapiro DB. Mechanisms of hemolysis-associated platelet activation. *J Thromb Haemost* 2013; **11**: 2148–2154.

DOI: 10.1002/ehf2.13393