

EDITORIAL

Phosphodiesterase-5 Inhibitor Therapy for Left Ventricular Assist Device Patients: More Data, More Questions

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Since the first reported experiences with left ventricular assist devices (LVADs), prevention of hemocompatibility-related adverse events (pump thrombosis, thromboembolism, or bleeding) has been critical for patient management. Unfortunately, even in the contemporary era, ≈50% to 60% of patients will have experienced a hemocompatibility-related adverse event after 1 year of device support.¹ Although the HeartMate 3 (Abbott) has significantly reduced the risk of pump thrombosis relative to older devices, 2-year risks of stroke (10%) and gastrointestinal bleeding (27%) remain undesirably high,² and effective medical therapies to further reduce complications have remained elusive.

See Article by Xanthopoulos et al.

One potential therapy garnering recent interest is phosphodiesterase-5 inhibitors (PDE5i), which are commonly used off label for treatment of pulmonary hypertension caused by left heart disease and right heart failure (RHF) in LVAD recipients. PDE5i potentiates PKG (protein kinase G)-mediated vascular smooth muscle cell relaxation by blocking the breakdown of cGMP.³ Since the 1980s, it has been known that this pathway is also present in platelets, where cGMP-activated PKG prevents release of calcium and thromboxane, inactivates surface glycoproteins, and triggers cytoskeletal changes that interfere with platelet

aggregation (Figure).⁴ PDE5i increase intracellular concentrations of cGMP, potentiating the PKG pathway, resulting in an antithrombotic effect.

Sildenafil, the most commonly used PDE5i, has been associated with a reduced risk of LVAD pump thrombosis and ischemic stroke in single-center analyses^{5,6}; however, confirmatory data from larger cohorts are lacking. In this issue of the *Journal of the American Heart Association (JAHA)*, Xanthopoulos et al report their analysis of the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), in which they examined the association between postoperative PDE5i use and the risks of pump thrombosis, stroke, gastrointestinal bleeding, and mortality.⁷ Over 4 years of follow-up, postoperative treatment with PDE5i was associated with a lower risk of the composite of pump thrombosis or ischemic stroke (adjusted hazard ratio [aHR], 0.84; 95% CI, 0.77–0.91) and a lower risk of all-cause mortality (aHR, 0.86; 95% CI, 0.79–0.93). Interestingly, these benefits appeared limited to patients who initiated PDE5i within 6 months of LVAD implantation, although the reduction in ischemic stroke did not manifest until after 12 months. Conversely, the risk of gastrointestinal bleeding was higher among PDE5i-treated patients (aHR, 1.14; 95% CI, 1.06–1.23).

As with all observational data analyses, there were important differences between treatment groups, with PDE5i-treated patients more likely to have preoperative renal disease, pulmonary hypertension, and right ventricular dysfunction. To mitigate the risk

Key Words: Editorials ■ bleeding ■ left ventricular assist device ■ phosphodiesterase inhibitor ■ stroke ■ thrombosis

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

For Sources of Funding and Disclosures, see page 3.

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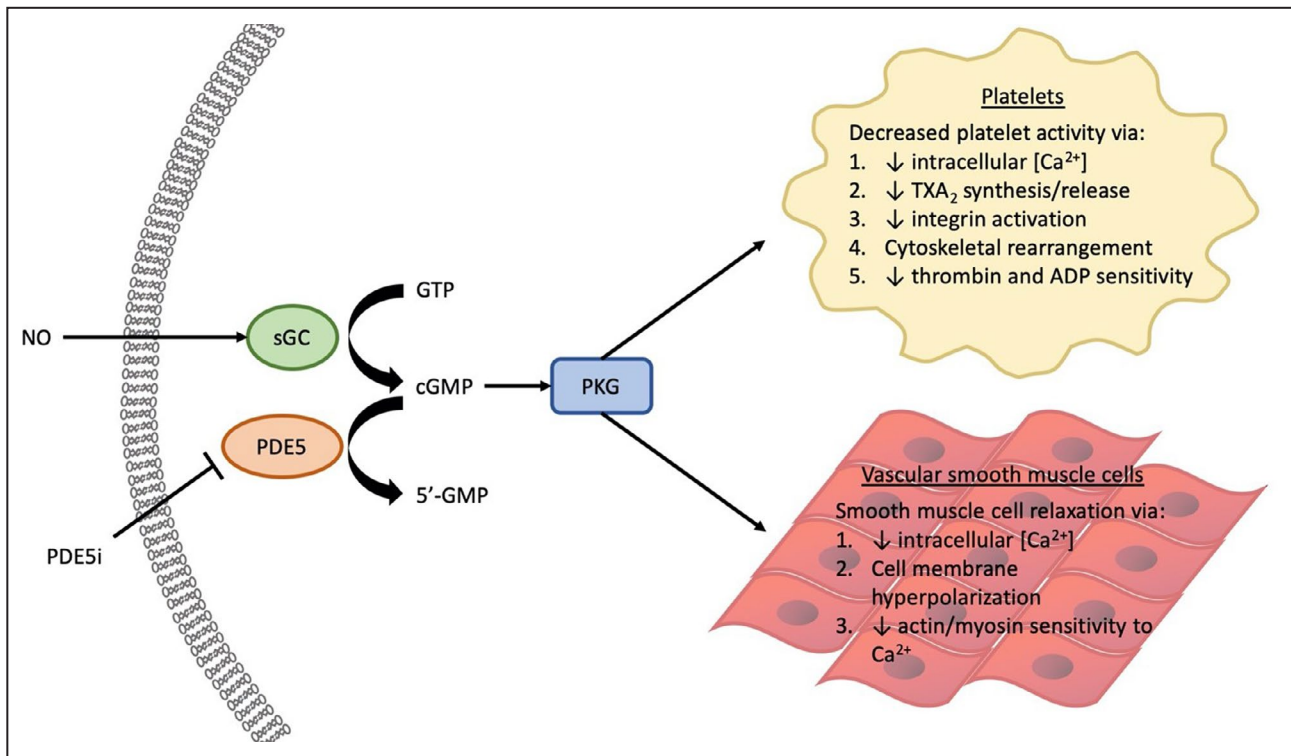


Figure. Phosphodiesterase-5 inhibitors (PDE5i) decrease platelet activity and promote vascular smooth muscle cell relaxation. Soluble guanylate cyclase (sGC) catalyzes the production of cGMP from GTP in a NO-mediated manner. cGMP activates PKG (protein kinase G), which promotes smooth muscle cell relaxation, and inhibits platelet activation and aggregation. PDE5i increase PKG activity by inhibiting the breakdown of cGMP to 5'-GMP. TXA_2 indicates thromboxane A2.

of confounding from these and other differences, the authors used a robust statistical method, known as inverse propensity of treatment weighting. They also took care to demonstrate similar intensity of antithrombotic therapy throughout follow-up between the 2 groups. Ultimately, the results of their analysis expand our understanding of potential indications for PDE5i beyond treatment of pulmonary vascular disease and RHF to include potential prevention of thromboembolic complications.

We congratulate Xanthopoulos et al⁷ for their valuable contribution to this area, in which more rigorous data on the risks and benefits of PDE5i use in LVAD recipients are urgently needed. Although these data are provocative, they need to be considered in light of some limitations. The timing of PDE5i initiation among treated patients was not described, so the timing of events relative to PDE5i treatment is unknown. In addition, the inverse propensity of treatment weighting method relied on preoperative characteristics, not characteristics at the time of PDE5i initiation. Although using postoperative characteristics would be challenging given the variability in time of PDE5i initiation across the cohort, balance between groups on important postoperative characteristics, such as renal function, cannot be assessed. Finally, although

elevated blood pressure is a risk factor for stroke in LVAD patients,⁸ these data are not routinely collected in INTERMACS and longitudinal blood pressure measurements cannot be adequately compared between groups.

The results from Xanthopoulos et al⁷ leave us with several unanswered questions. First, is the association between PDE5i use and lower thrombotic risk causal? Although there is a plausible mechanistic explanation, PDE5i use has not previously been linked to decreased stroke risk in other populations, such as pulmonary arterial hypertension or heart failure with preserved ejection fraction. The incidence of stroke, however, is lower in these populations, and stroke rates were not specifically reported in trials of PDE5i in these settings.^{9,10} Given that the thrombotic risk is greater in LVAD patients, the possibility remains that an antithrombotic effect may become more evident in this higher-risk cohort.

Second, if the association with lower thrombotic complications is causal, what is the mechanism by which this is achieved? The in vitro effects of sildenafil on platelet function suggest that an antiplatelet effect could be the predominant mechanism; the nearly equal increase in gastrointestinal bleeding risk in this analysis, as well as a previously observed increase in bleeding events

associated with PDE5i therapy,¹¹ supports this hypothesis. One might ask, if the potential benefit of PDE5i is related to antiplatelet activity, should we instead be evaluating alternative antiplatelet strategies, such as dipyridamole and P2Y12 antagonists, for mitigation of stroke risk, rather than relying on a pleiotropic effect of PDE5i? This direction, however, is contrary to current efforts to evaluate the role of decreased platelet inhibition, such as the ARIES (Antiplatelet Removal and Hemocompatibility Events With the HeartMate 3 Pump) clinical trial. This trial will evaluate the role of withholding antiplatelet therapy to reduce bleeding events, given the low incidence of LVAD thrombosis observed with this device.

The authors propose a potential alternative mechanism, related to improvement in right ventricular function with resultant increases in LVAD flow. Should this be the case, similar associations would be anticipated with other therapies augmenting right ventricular function. Although digoxin therapy has been associated with a reduction in gastrointestinal bleeding risk,¹² a reduction in thrombotic risk has not been reported. It will be interesting to evaluate the impact on thrombosis and bleeding associated with other pulmonary vasodilators that lack an antiplatelet effect, such as endothelin-receptor antagonists. Data forthcoming from the SOPRANO (Clinical Study to Assess the Efficacy and Safety of Macitentan in Patients With Pulmonary Hypertension After Left Ventricular Assist Device Implantation) trial may help to address some of these questions.

Third, what does the increased risk of bleeding observed herein and in other analyses mean about the risk of PDE5i therapy among LVAD patients awaiting heart transplantation? If this a causal relationship, long-term PDE5i use may similarly increase bleeding risk at the time of heart transplantation. Currently, data on the safety of using PDE5i in patients undergoing heart transplantation are limited to case series or small single-center studies. There is a pressing need to explore this question in a prospective manner.

Fourth, the net clinical impact of PDE5i requires further study. Given that the risk of pump thrombosis has been significantly reduced with the latest-generation devices (which are underrepresented in the cohort analyzed herein), the potential antithrombotic benefit of PDE5i in future patients will likely be limited to a reduced risk of stroke. This is still important, as stroke is arguably the most devastating LVAD complication, and even nondisabling strokes can reduce survival.¹³ However, if the decreased mortality risk was partially driven by a reduction in pump thrombosis events, this risk decrease may be attenuated in future patients in whom pump thrombosis risk is lower. Furthermore, PDE5i therapy has been associated with increased risk of RHF, a strong correlate of increased mortality, in other INTERMACS analyses.^{11,14} It therefore seems

unlikely that the mortality benefit is attributable to improvements in rates of RHF. Last, additional research is needed to also understand the impact of these drugs on other patient-centered outcomes, such as functional capacity and quality of life.

Finally, the results from Xanthopoulos et al⁷ are striking for yet another reason: 35% of patients were treated with PDE5i at some point while on LVAD support, a remarkably high proportion for a treatment without prospective data to support its use. Indeed, most medical therapy in LVAD patients is supported by limited data. Although engineering to improve hemocompatibility continues to advance, there has been less progress made in improving the medical management of LVAD recipients to mitigate the risk of adverse events. Most data on medical therapies come from observational studies and have not led to widespread changes in practice. However, the PREVENT (Prevention of HeartMate II Pump Thrombosis Through Clinical Management) and the ENDURANCE (A Clinical Trial to Evaluate the HeartWare Ventricular Assist System) supplemental trials demonstrated that positive prospective data can quickly lead to widespread adoption.^{15,16} Ongoing work is still needed, however, because the applicability of these findings to new devices is unknown. Devices have unique hemocompatibility and hemodynamic profiles that extend beyond the centrifugal versus axial flow dichotomy and may require unique management strategies.¹⁷

As these authors note, this study should serve as yet another call to arms to prospectively study interventions to reduce LVAD-specific complications. Prospective research in this population is admittedly challenging, given the relatively small population. But, with rates for many complications remaining at 10% to $\geq 20\%$ within 12 to 24 months, there is a continued need to identify better management strategies for stroke prevention, gastrointestinal bleeding, residual RHF, and infectious complications. Only with further reduction of adverse events can we expand the use of LVAD therapy to help a broader population of patients with heart failure live longer and better.

ARTICLE INFORMATION

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Sources of Funding

Dr Gulati is supported by NIH grant 1F32HL149251-01.

Disclosures

Dr Kiernan reports the following: Medtronic: Clinical Trial Steering Committee, Scientific Advisory Board, and speaking honoraria. Dr Gulati has no disclosures to report.

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