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EDITORIAL COMMENT

You do something to me, something deep inside

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This article refers to 'Platelet activation is a preoperative risk factor to the development of thromboembolic complications in patients with continuous-flow left ventricular assist device' by F. Consolo *et al.*, published in this issue on pages xxx.

The use of left ventricular assist devices (LVAD) in a much broader population has led to a linear increase in implantation rates in the last decade.[1] Due to improvements in technology and better care, survival rates increased significantly, but thromboembolic stroke remains a feared complication in patients assisted by an LVAD. A vast majority of these strokes occur despite adequate anticoagulation and even with the new magnetically levitated devices, stroke rates are still high.[2] It is currently insufficiently clear how stroke can be prevented in these patients as no phase III clinical trials on anticoagulation in patients with LVADs have been performed. A systematic review on the relation between anticoagulation protocols and occurrence of stroke after LVAD implantation found that platelet aggregation inhibitors are the most important in preventing thromboembolic stroke and should be part of the anticoagulation protocol.[3] Antiplatelet therapy might even be sufficient without the addition of coumarins, but this should be supported by a qualitative assessment of the coagulation status such as thromboelastometry and platelet function assays besides the classical parameters [i.e. international normalized ratio (INR), activated partial thromboplastin time (aPTT), and platelet count]. With such information, it would be possible to calibrate the antithrombotic therapy, deciding dose variation or withdrawal of either anticoagulant or antiaggregant therapy, on a mechanistic basis. On the other hand, the most routinely used antiplatelet, acetylsalicylic acid, had limited ability to prevent shear stress-mediated platelet activation (SMPA) for platelets subjected to elevated shear via cyclic passage through a continuous-flow ventricular assist device operating under normal clinical conditions (speed, flow rate).[4] Although these were *in vitro* experiments and purified platelets instead of whole blood were used, it may indicate that combinational drug strategies or new agents are still warranted in preventing thromboembolic complications in LVAD patients.

Both inpatient and device complications remain a challenge for bioengineering. Advances in device technology may be even more important than anticoagulation regimes as preclinical studies in LVAD technology demonstrates that design changes may offer a more robust alternative to antiplatelet drugs.[5] With more sophisticated devices at least the routine use of combined antiplatelet therapy and coumarins bridged by postoperative heparin is now questioned. Postoperative heparin seems not to decrease the number of thromboembolic events after axial continuous-flow LVAD implantation and may increase the risk of short-term systemic bleeding complications and rethoracotomy.[6–8]

In the HeartMate III (HM3) era, with less fear for in-pump thrombosis (but not a decreased number of thromboembolic events after 6 months),[2] an anticoagulation regime with reduced INR/aPTT targets may be more than ever suitable, but unfortunately these parameters are poor predictors for either platelet function (obviously) or thromboembolic complications. Reducing anticoagulation or alternative anticoagulant drugs might result in fewer bleeding complications and ultimately better outcomes. However, that leads us being between Scylla and Charybdis as proof beyond doubt is missing that pump thrombosis or thromboembolic stroke does not increase with less anticoagulation. So rigorous evaluations of anticoagulation use in LVAD patients are needed, since practices vary widely. However, it may well be that there is no ideal anticoagulation protocol that fits every patient. For that matter, it would be most helpful to determine patients at risk for thrombotic complications.

In this issue of the Journal, Consolo and co-workers present the results of a single-centre cross-sectional study with a duration little over 2 years that used the Platelet Activity State (PAS) assay to determine SMPA and correlate this with the occurrence of thrombotic events, in this case restricted to pump thrombosis and thromboembolic stroke.[9] They measured SMPA pre-implant and 1, 3, 6, 12, 18 and 24 months thereafter and found that

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thrombotic events are associated with both baseline PAS and elevated PAS values at the time of the thrombotic event. PAS did not increase significantly in the overall LVAD population over time. All patients had combined anticoagulation therapy at the time of the event. In patients who eventually developed a thrombotic event, pre-implant PAS values were higher, which might suggest that the observed thromboembolic complications were related to a possible pro-thrombotic profile of these patients at baseline, rather than the anticoagulation protocol followed after implantation.

The limitations of the study are obvious. During the study period three different pumps were used [HVAD, HeartMate II (HM2) and HM3] in 68 patients and only 6 events occurred; all except one in the HVAD. One pump thrombosis occurred in the HM2 pump and no stroke occurred in either HeartMate devices. That puts a strong limitation to the generalizability of the findings. Furthermore, the statistics only show an association between elevated PAS and thrombotic events, and cannot point towards a causal relationship. Also, it is unclear if, apart from pre-implant, elevated PAS occurred at the day of the thrombotic event or days prior to the event and could really be used as a warning sign similar to lactate dehydrogenase elevations that are frequently observed prior to pump thrombosis.

The absence of any stroke in the HM2 and HM3 is striking. Presented numbers for the HM2 device range from 0.03–0.31%/patient/year for thromboembolic stroke alone. This may be caused by the used definition. A stroke event was defined according to INTERMACS as a neurological deficit lasting more than 24 h or less than 24 h with a brain imaging study showing new infarction. In particular, ischaemic stroke was defined as the new appearance of a hypodense image on non-contrast cerebral computed tomography (CT) whose location is compatible with clinical signs and symptoms. The use of this definition has several consequences. Transient ischaemic attacks (TIAs) or minor strokes are missed with this approach as CT is actually known to have a limited sensitivity when it comes to detecting acute cerebral ischaemia. As a result in some patients with clinically suspected stroke the CT images may not reveal a stroke since ischaemic sites might take time to become noticeable or hypodensities might be too small to be visualized. That might be arguable as TIAs are clinically less relevant, but for a mechanistic approach they should be included. The patient was just lucky that the embolus resolved in time or was not large enough to cause permanent sequelae.

Apparently no haemorrhagic strokes occurred and the four strokes (all in the HVAD device) were considered thromboembolic. However, differentiation between thromboembolic and haemodynamic stroke may be challenging in some patients as low cerebral perfusion may cause cortical infarcts which may appear embolic in origin.

Finally, one-quarter of the patients were on veno-arterial extracorporeal membrane oxygenation (VA-ECMO) before LVAD implantation and all patients with a thrombotic event had an intra-aortic balloon pump ($n = 3$), an Impella ($n = 1$) or VA-ECMO ($n = 3$), or a combination of these devices and it is unclear if these devices has had an impact on the pre-implant PAS values. Each of these mechanical circulatory support devices is associated with an increased risk of thrombotic events on its own.[10]

What remains is that PAS was significantly increased in patients with a thrombotic event compared to healthy volunteers. Furthermore, patients with a HM3 had no events and lower PAS values than patients with the other two devices, suggesting again that advances in bioengineering may be more important than anticoagulation regimes alone. As there were no events in the HM3 patients it is unclear if PAS is a useful tool in predicting thrombotic events. Even if this could be demonstrated in future prospective studies, it remains unclear by which means the heralded complication can be prevented. However, the findings of this study may be a first step to clarify the mechanism of thrombotic complications and towards a personalized anticoagulation regime.

From the patients' point of view, implantation of an LVAD does something to you, something deep inside. The affection for your LVAD may resemble that for a close friend. It compensates your heart failure, but the device has an effect on platelets and the associated thrombotic complications or the currently inevitable anticoagulation drugs to prevent it may have a detrimental effect on the brain. It will take some more steps in bioengineering or drug design before your heart mate will become your soul mate as well.

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References

1. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. *Eur J Heart Fail* 2017;**19**:595–602.
2. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, Pagani FD, Aaronson KD, Dean DA, McCants K, Itoh A, Ewald GA, Horstmanshof D, Long JW, Salerno C; MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med* 2017;**376**:440–450.
3. Backes D, van den Bergh WM, van Duijn AL, Lahpor JR, van Dijk D, Slooter AJ. Cerebrovascular complications of left ventricular assist devices. *Eur J Cardiothorac Surg* 2012;**42**:612–620.
4. Valerio L, Tran PL, Sheriff J, Brengle W, Ghosh R, Chiu WC, Redaelli A, Fiore GB, Pappalardo F, Bluestein D, Slepian MJ. Aspirin has limited ability to modulate shear-mediated platelet activation associated with elevated shear stress of ventricular assist devices. *Thromb Res* 2016;**140**:110–117.
5. Bluestein D, Girdhar G, Einav S, Slepian MJ. Device thrombogenicity emulation: a novel methodology for optimizing the thromboresistance of cardiovascular devices. *J Biomech* 2013;**46**:338–344.
6. John R, Kamdar F, Liao K, Calvin-Adams M, Miller L, Joyce L, Boyle A. Low thromboembolic risk for patients with the Heartmate II left ventricular assist device. *J Thorac Cardiovasc Surg* 2008;**136**:1318–1323.
7. Slaughter MS, Naka Y, John R, Boyle A, Conte JV, Russell SD, Aaronson KD, Sundareswaran KS, Farrar DJ, Pagani FD. Post-operative heparin may not be required for transitioning patients with a HeartMate II left ventricular assist system to long-term warfarin therapy. *J Heart Lung Transplant* 2010;**29**:616–624.
8. van den Bergh WM, Lansink-Hartgring AO, van Duijn AL, Engström AE, Lahpor JR, Slooter AJ. Thromboembolic stroke in patients with a HeartMate-II left ventricular assist device – the role of anticoagulation. *J Cardiothorac Surg* 2015;**10**:128.
9. Consolo F, Sferrazza G, Motolone G, Contri R, Valerio L, Lembo R, Pozzi L, Della Valle P, De Bonis M, Zangrillo A, Fiore GB, Redaelli A, Slepian MJ, Pappalardo F. Platelet activation is a preoperative risk factor to the development of thromboembolic complications in patients with continuous-flow left ventricular assist device. *Eur J Heart Fail* 2018. https://doi.org/10.1002/ejhf.1113.
10. Barge-Caballero E, Almenar-Bonet L, Gonzalez-Vilchez F, Lambert-Rodríguez JL, González-Costello J, Segovia-Cubero J, Castel-Lavilla MA, Delgado-Jiménez J, Garrido-Bravo IP, Rangel-Sousa D, Martínez-Sellés M, De la Fuente-Galan L, Rábago-Juan-Aracil G, Sanz-Julve M, Hervás-Sotomayor D, Mirabet-Pérez S, Muñiz J, Crespo-Leiro MG. Clinical outcomes of temporary mechanical circulatory support as a direct bridge to heart transplantation: a nationwide Spanish registry. *Eur J Heart Fail* 2017 Sep 26. https://doi.org/10.1002/ejhf.956. [Epub ahead of print]