Editorial

HeartMate 3—a "Step" in the right direction

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Earlier in this decade, the concerning reports regarding high rates of complications for left ventricular assist devices (LVADs) led to the interruption and finally the premature completion of the REVIVE-IT (Randomized Evaluation of VAD InterVEntion before Inotropic Therapy) trial (1). The discontinuation of this trial appeared to be a set back for mechanical circulatory support for less sick heart failure (HF) patients and a set back for (LVAD therapy in general. In contrast, the ROADMAP study provided a signal towards a beneficial effect of LVADs in the setting of intermediate INTERMACS (INTERagency registry for Mechanically Assisted Circulatory Support) categories (2).

These two studies were based on outcomes from commonly implanted LVADs, namely the HeartMate2 (HM2: Abbott Labs; Lake Bluff, IL, USA) and Heartware (Medtronic Inc; Minneapolis, MN, USA). Therefore, further advances in MCS therapy are predicated on developing a better device that provides improved clinical outcomes with fewer adverse events. The HeartMate 3 (HM3), a fully magnetically levitated circulatory pump, is a possible step forward (3).

The pulsatile flow HeartMate XVE phased out of clinical use in 2009–2010 (4) and was replaced by the continuous axial flow HM2. Smaller, lighter, and much more durable, the HM2 was rapidly adopted and implant rates soared (5,6). The HeartWare HVAD joined the market only a few years later with a continuous centrifugal flow design. Comparisons between the new continuous flow pumps and the XVE pulsatile pump identified several complications specific to continuous flow technology, including aortic insufficiency (AI) (7) and gastrointestinal (GI) bleeding (8,9).

The HM3 was designed to address these issues by adding intermittent speed reduction to a continuous centrifugal flow design. This unique software algorithm provided for artificial pulsatility. In addition to the artificial pulse, the HM3 provided full magnetic levitation, textured interior surfaces and larger gap spaces within the pump housing all with the aim of improving biocompatibility (10).

In the MOMENTUM3 trial, we are able to look at what this technological upgrade could represent from a clinical standpoint (11,12). In this study, short term outcomes (six months) of 294 patients are presented. 152 were assigned to the new centrifugal-flow pump group (HM3) and 142 to the axial-flow pump group (HM2). The primary end point was a composite of survival free of disabling stroke or survival free of reoperation to replace or remove the device (for reasons other than recovery) at six months after implantation. Secondary end points included the frequency of adverse events; actuarial survival; functional status; and quality of life.

The primary objective of the trial was to show the non-inferiority of the centrifugal-flow pump to the axial-flow pump with respect to the primary endpoint measure at six months after implantation. A pre-specified analysis allowed for a superiority determination if the primary non-inferiority status was confirmed (10).

The trial met its primary endpoint and in fact, the HM3 device was found to be superior to the HM2, primarily due the lack of reoperation for pump thrombus. Incredibly, there were no reported pump thrombus events in any patient who received a HM3 device. Unfortunately, there

were no significant differences between the two pumps in the rates of other major complications, including right heart failure, stroke, major infection or bleeding episodes, particularly gastrointestinal bleeding.

The absence of suspected or confirmed pump thrombosis with the centrifugal-flow pump was similar to the results with the same device in the nonrandomized CE Mark study (13). A recent analysis has also shown that the centrifugal-flow device does not cause loss of high-molecular-weight multimers of von Willebrand factor to the same degree that the axial-flow pump does (14).

An unanswered question relates to the mechanism underlying the apparent better biocompatibility of the HM3. Is it the engineering design of the pump housing with the larger gaps in the blood flow path or is it the software algorithm resulting in an artificial pulse? Does the pulse cause washing and therefore prevent thrombus formation?

Importantly, pulsatility with continuous flow devices is not an all or none phenomenon. Most patients with continuous flow LVADs have some degree of arterial pulsatility, leading many to discourage the term "non-pulsatile" (15). Pulsatility may result from blood ejected through the aortic valve or transmission of the systolic pressure wave through the LVAD (in cases of a closed aortic valve). The HeartMate II and HVAD both identify changes in power (and corresponding flow) during systole and diastole using a pulsatility index. This index reflects ventricular contractility and correlates with the pulse pressure on arterial pressure tracings. Newer reports indicate this measure of pulsatility is inversely related to GI bleeding, i.e., patients with a higher pulsatility demonstrate lower incidences of GI bleeding (16-18). Since the artificial pulse in the HM3 is not synchronized with patient heart rate, it may augment or diminish the native pulse.

Another benefit of HM3 pulsatility would relate to aortic insufficiency (AI). The development of aortic insufficiency while on mechanical support can be debilitating and life threatening. The result is a decrease in net forward flow, increased LV distension, and a return to heart failure. One strategy to avoid this complication has been to adjust LVAD speed (and corresponding flows) down in order to better fill the ventricle and enable ejection through the aortic valve. This is a potentially dangerous strategy; however, because it risks a return to a low cardiac output state if the patient's ventricle can't keep up with the added workload. In addition, lower pump speeds may predispose to pump thrombus. Another strategy involves just the opposite management: increasing LVAD speed. The theory is dependent upon a fixed regurgitant lesion (which may not be true) and thus increasing LVAD speed and hence output would compensate for the proportion of output that returns to the LVAD. However, if there is a dynamic component to the regurgitant lesion, then increasing LVAD speed would decrease LVEDP further and therefore exacerbate the degree of aortic insufficiency.

While the prevalence of AI remains variable in the literature, any design modifications that can attenuate the development of aortic valve fusion would be beneficial (7). It is possible that HM3 pulsatility permits intermittent aortic valve opening, thereby preventing cusp fusion and the subsequent development of aortic insufficiency.

More recent studies have identified lower blood pressure as protective from the development of aortic insufficiency (19). Additionally, strict blood pressure control is increasingly recognized as a therapeutic goal to reduce the rates of hemorrhagic and embolic stroke (20,21). Will a more focused effort on blood pressure control also improve pulsatility, thereby preventing both GI bleeding and the development of aortic insufficiency? Will the artificial pulse be helpful in all LVAD patients, or can we identify a subgroup of patients that are most likely to benefit?

Regarding anticoagulation, the ultimate goal for any circulatory support device would be to achieve a level of biocompatibility that would obviate the need for any antiplatelet or anticoagulant medication. Full magnetic levitation eliminates the need for a mechanical or hydrodynamic bearing and by providing large gaps in the blood flow pathway, the stimulus for thrombus formation should be reduced. Texturing of the pump lining with sintered titanium microspheres may also promote the formation of a biologic barrier to further help decrease the risk of the thrombosis (22). In spite of these engineering improvements, anticoagulation protocols for the HM3 CE Mark trial were similar to those in the HeartMate II bridge-to-transplant (BTT) study. The trial sponsor recommended post-operative heparin until achievement of a therapeutic INR with warfarin in addition to daily aspirin. The crucial question is whether or not the new design features of the HM3 will allow clinicians to reduce anti-thrombotic therapy to levels that significantly reduce bleeding episodes. Unfortunately, the early results of MOMENTUM3 fail to demonstrate any meaningful reduction in bleeding or neurologic events (12).

Astonishingly, there remains no reported incidence of pump thrombus between the CE Mark and MOMENTUM3 trials. This may give clinicians confidence

to reduce anticoagulation targets in those patients at low risk for stroke and/or at high risk of GI bleeding.

Cessation of anticoagulation therapy has been assessed in the TRACE study (23). In TRACE, 100 HeartMate II patients with were enrolled and followed for one year with reduced anti-thrombotic medications. The surprising finding of TRACE was that the incidence of device thrombosis was uncommon at 4%, but 40% of patients off all anti-thrombotic medications continued to have bleeding complications. Therefore, certain recipients of CF-LVADs are at high risk for bleeding episodes regardless of the intensity of anticoagulation. Further research will help to identify these patients and perhaps provide clinical rationale for minimal anticoagulation in HM3 recipients with the comfort that this risk of pump thrombus will be low.

REMATCH was published in 2001 and represented a 68 patients experience with a pulsatile pump that suffered from limited durability by current standards (4). The HeartMate2 and ADVANCE trials evaluated the next generation of continuous-flow devices and were reported less than a decade later, recruiting 133 and 140 patients respectively (24,25). Momentum 3 will enroll over 1,000 patients and will define the contemporary clinical results associated with state-of the art mechanical circulatory support (11). The history of mechanical circulatory support is now being characterized by larger, and more frequent technological advances: each step leading to improved outcomes for patients with end-stage heart disease.

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Footnote

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