Editorial

The evolution of left ventricular assist devices—a moment to reflect

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In the Mechanical Circulatory Support Therapy with HeartMate 3 trial (MOMENTUM 3) Mehra *et al.* compared the outcomes of death and disabling strokes in 294 patients six months after implantation of the latest generation of left ventricular assist devices (HeartMate III) to patients treated with the former generation of the same manufacturer (HeartMate II, Thoratec/St Jude Medical) (1). The primary combined endpoint was survival free of disabling strokes or survival free of reoperations to replace or to remove the device at six months after implantation. No significant differences in mortality and disabling strokes were seen, but the rate of reoperations for malfunction was lower in the group of patients receiving the HeartMate III [1 (0.7%) *vs.* 11 (7.7%); hazard ratio: 0.08; 95% CI, 0.01 to 0.60; P=0.002]. The higher rates of reoperations were therefore the main driver not only for the statistically noninferiority, but also for the superiority of HeartMate III compared to HeartMate II for this particular outcome parameter. No events of suspected or confirmed thrombosis were reported in the HeartMate III group compared to 18 events in 14 (10.1%) patients treated with HeartMate II (P<0.001).

HeartMate III is a third generation centrifugal continuous-flow LVAD with the rotor being suspended in the blood flow using a noncontact design through magnetic levitation. It has received the European CE Mark approval in 2014. The main advantages of this type of system are the noncontact bearings. This design idea together with wide blood flow gaps within the pump is thought to reduce heat formation, friction and shear stress and such should reduce the possibility of thrombus formation. In addition, the device facilates rapid changes in pump-speed to modulate an artificial puls. The smaller size of the device eliminates the need for extensive tissue dissection or an abdominal pocket at the time of implantation. In the HeartMate III CE Mark trial Zimpfer *et al.* described the 30-day outcome in 50 patients receiving HeartMate III as bridge to transplant (BTT) or destination therapy (DT) (2). Here, no events of thrombosis were reported, however two patients developed a stroke. The 1-year outcome for the same patient cohort was recently presented at the International Society for Heart and Lung Transplantation Scientific Sessions in 2016. After one year, no patient developed a pump thrombosis, but six patients developed a stroke in the first six months and three in the following (3).

The HeartMate II is a second generation LVAD that is using a continuous flow pump delivered by a rotor suspended in the blood flow through mechanical bearing and has been approved by the US Food and Drug administration (FDA) for BTT in 2008 as well as DT in 2010. The advantages of second generation pumps were a reduction of moving parts compared to the first generation with a resulting reduction of thrombosis, infection and mechanical failure. The risk of thrombosis associated with HeartMate II has recently been examined by Starling *et al.* who found an increase of pump thrombosis to of 8.4% at three months after implantation as compared to the initial trial that led to FDA approval of the device in 2008

(thrombosis rate 1.6%) and 2010 as (thrombosis rate 3.8%) (4). In correspondence to Starling's article, increased rates of pump thrombosis were not experienced by other European leading implanting centres such as Hannover, Germany and Innsbruck, Austria (5). Using data from the registry for Mechanically Assisted Circulatory Support (INTERMACS), Kirklin *et al.* described a rate of pump thrombosis of 6% at six months in HeartMate II devices implanted between 2010 and 2013 (6). However, the trend of increasing pump thrombosis was not seen and indeed declined, when Kirklin *et al.* extended the data examination through to June 2014 (7).

Another third generation LVAD is the HeartWare HVAD system (Medtronic), which has been approved by the FDA as BTT in 2012. The ENDURANCE trial compared 446 patients receiving a HVAD as DT therapy to treatment with HeartMate II (8). After a follow up period of two years, more strokes (29.7 % *vs.* 12.1%) were observed in the group treated with a HVAD, however there was no difference in overall survival (55.4% *vs.* 59.1%; absolute difference, 3.7%; 95% upper confidence limit, 12.56 percentage points; P=0.01 for noninferiority).

Broadly, causes for the development of pump thrombosis can be divided into intrinsic pump failure (e.g., heat generation, shear stress, device design, coating), patient related causes (e.g., non compliance, procoagable state, infection, existing thromboembolic disease) and therapy related causes (e.g., management and monitoring of anticoagulation, follow up structure, treatment of infection, support of patients, pump speed setting, operative procedures).

Preventing thrombosis is achieved by anticoagulation with a combination of Vitamin K antagonists (e.g., warfarin) titrated to an INR target of 2.0–3.0 and a platelet aggregation inhibitor (e.g., aspirin 100 mg a day). As a consequence bleeding complications can be seen as a common sequelae of therapy.

In one of the earlier trials from 2009, the HeartMate II was compared to a first generation pulsatile device, the HeartMate XVE in 200 patients and followed up over a two-year period (9). The HeartMate II achieved a better primary outcome defined as survival free from disabling strokes and reoperation to repair or replace the LVAD {62 patients [46% (95% CI, 38–55)] versus 7 patients [11% (95% CI, 3–18)], P<0.001}. However, the bleeding rates have been reported to be as high as 81% in the HeartMate II group versus 76% in the HeartMate XVE group (P=0.06; defined as requiring at least two units of packed red blood cells) and 30% versus 15 % respectively (P=0.57; defined as requiring surgery). In the current MOMENTUM 3 trial the overall bleeding rates were 33.1% in the HeartMate III group versus 39.1% in the HeartMate II group [relative risk 0.85; 95% CI, 0.62–1.15, P=0.29) (1).

Looking forward, the MOMENTUM 3 trial has recently been extended (NCT02892955) and aims to enrol over 1,000 patients to further examine the long-term outcome for patients with HeartMate III with the clear aim to obtain FDA approval for BTT and DT. The results of this extended trial can be expected by 2019.

Not only is the number of patients with severe heart failure expected to increase but also the number of LVAD implants are expected to rise worldwide (10,11). Since the first generation of LVADs, modern implantable systems have clearly improved. The mortality in the early trials was 52% after one year compared to 25% with medical therapy (12). Since then mortality has further declined and with second generation continuous-flow pumps the survival has increased to 80% at 1 year and 70% at 2 years (11). Reducing pump thrombosis and tackling the disabling strokes will be a major focus in the design and development of these exciting life extending devices. Further fields of improvement would include miniaturizations, removal of external drivelines, integration of haemodynamic monitoring and telemetry.

The future looks bright for the treatment of advanced heart failure.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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