

SIMON

I'm Dr. Simon Maltais, and this presentation will be about discussing how can we prevent the revolution of LVAD therapy, and this will be a surgeon's perspective. This is my disclosure slide. I will be discussing off label use of the HeartWare device.

MALTAIS:

So the objective of this presentation is to understand the diversity of long term complications associated with the durable LVAD implantation, evaluate the physiologic differences of available durable devices, and potentially their potential impact on pump selection patient related outcomes, measure the impact of anti-coagulation in LVAD patients, and potentially risk factors for thromboembolic events, and then review the concept of hemocompatibility and related outcomes.

So because this is a surgeon's presentation, we'll cut to the chase and say that we may not have reached the perfect pump, but we are closer. We still need to gather data, a good one, and then we'll try to really emphasize that pump is only one dweller in a very complex system.

So Steve Jobs said, that "Design is a funny word. Some people think design means how it looks. But of course, if you dig deeper, it's really how it works." And we'll try to, again, speak to that during the presentation and to go over design and function and what that represents for patients.

As you can see on this slide here, the designs have changed over the years from larger pulsatile devices to smaller, even percutaneous devices, that are now mostly non-pulsatile. Survival with these devices is now, as opposed to before, an expected outcome. So patients are expected to survive with these devices, and the average survival for any devices that now reaches the market has to be about 80% plus one year.

But we've created with these devices that are now mostly non-pulsatile, what I like to call a continuous flow pump disease, where when we implant these pumps, they can clot. And it will create a need for anti-coagulation. There's an increased risk of thromboembolism like stroke, renal infarct, skimming bowel, heart attack, risk of infection by the nature of the drive line that we insert that patients are dependent on, like drive line infection or pocket infection.

Because the pump isn't in constant contact with the patients, there is a significant degree of hemolysis, and what we describe as acquired von Willebrand syndrome, that will make patients at risk of having complications, like bleeding. And the non-physiologic nature of blood flow into the ascending aorta, non-pulsating blood flow will create progressive root dilatation, aortic valve closure, aortic valve leaflet and fusion, and potentially even aortic valve regurgitation.

Furthermore, a the low pulsatile nature of the pump will create AV malformation, GI bleeding. And this interacts with patients, and patients' sex, patients' age, BMI, prior history of cardiac disease, and all these things are in complex interaction. And to three important spheres.

What we'll talk about in the next few slides here is that complex interaction within the pump, the provider, and the patient himself. Let's start with the pump. So we've seen important changes in technology. And this technology now has evolved to which there's three continuous flow pumps that are approved for either bridge to transplant, the HeartMate II, the heart wear, now the HeartMate III, or the destination therapy, the HeartMate II.

These evolve from bearings to bearings [INAUDIBLE] and now bearing less pumps with magnetic and hydrodynamic levitation. And this technology has translated into advances in outcomes in patient survival improvement. You can see here as opposed to medical treatment, the initial pulsatile flow pumps have improved survival, not to the extent where early and most recent experience with continuous flow pumps have advanced the field.

The event profile also has changed and has improved with continuous flow pump technology. You can see here that the mechanical reliability has improved, the infection rate has improved, the degree of RV failure has improved, the rate of stroke, as well as rate of bleeding has all improved with advances in technology.

While the pumps have improved survival, the physiologic impact of these pumps is vastly different. There's a wealth of literature supporting this. And these pumps are different in many different areas, from an unloading perspective to hemocompatibility. And we've talked about hemolysis profile.

So the physiologic differences exist. And so this translates into patient outcome differences. Now we know that the pumps are now expected to provide survival in our patients. But we now have different physiologic impact. And this is very different for both [INAUDIBLE]. There's a wealth of literature supporting this. They are different in many different areas from loading and hemocompatibility standpoint, and we've talked about hemolysis profile.

And there are physiologic differences, and this leads to patients' outcome differences. So if we look at von Willebrand degradation, which is a marker of hemolysis, you can see here this is data we've presented at ISHLT in 2016. When we compare patients with HeartMate II and HeartWare one and three months post-implant, you can see here that the rate of degradation or hemolysis is greater in patients with HeartMate II as opposed to HeartWare

So what do we know so far? There are major physiologic differences. There's different compatibility. We've talked about this. And now how does this translate into clinical outcome? Well, if we look at the HeartWare bridge to transplant trial, comparing the pump in the study group, HeartWare, to the control group HeartMate II, you can see here that there are significant differences in terms of pump replacement. You can see it in this study group there seems to be less pump replacement, so potentially improvement in design. But while the pump replacement seems to be lower, the rate of stroke, both ischemic and hemorrhagic is higher, with the HeartWare pump.

In the HeartMate III trial, so HeartMate III versus HeartMate II, centrifugal versus axial flow pump, you can see here that the event free survival is improved now with the HeartMate III. But when we dig more deeply into looking at what sort of differences exist between these patients, you can see that the axial flow pump perhaps increases thrombosis. But patients in the HeartMate III group perhaps have a trend towards increased risk of disabling stroke.

So let's look at patients. Is there a difference by sex and race when it comes to implanting the devices in patients with the HeartWare device? This is data from the bridge of transplant and continued Access Protocol for the HeartWare device. You can see here as while HeartMate II and HeartWare have depicted similar survival, women are perhaps an increased risk of RV failure, interlopes, RVAD, respiratory failure as well as renal failure.

Let's look at lower body surface area. So patients with lower body surface area are at an increased risk a complication with patients refusing HeartMate II. As you can see here, appears to be true in patients that received the HeartMate II, the BSA less than 1.9 seems to be associated with a survival of 43% as opposed to 83% at one year in these patients.

So again, the importance of understanding what sort of implications and what sort of co-morbidities have an impact on patient outcome and the choice of pumps over time. Does the ideology of heart failure is important, so we looked this in our research network. And you can see here patients with the ischemic, non-ischemic ideology of heart failure have different outcomes in terms of risk of stroke over time.

When you look at the predictors of stroke, patients having an HVAD as opposed to HeartMate II is an increased risk of stroke over time. So again, mitigating perhaps the choice of HeartMate II in patients with previous history of stroke or a greater risk of stroke, perhaps with advanced age.

So it's important to choose the right pump. Tailoring the pump therapy is based on numerous factors, and this will continue to stay true with the newer technology like HeartMate III. Device therapy could be optimized in various pump population. And this will lead to enhanced late outcomes.

Let's look at provider and again Steve Jobs would say, that it's important to make mistakes, but don't repeat them, and this will lead to improvement in your innovations. When you look at the HeartMate II experience, while patients were doing much better with this newer continuous flow pump technology, whereas we were dealing with still bleeding and so the recommendation have evolved to say, well, if we're dealing with bleeding, and we have still strokes, we need to reduce INR goal perhaps, and keep it between 1.5 and 2.5, as opposed to 2 and 3.

This led to this complication, and we know that relaxing anti-coagulation in patients have evolved to a spike in HeartMate II thrombosis towards the late 2012. And this has led to this New England Journal paper, which has reported unexpected abrupt increase in less ventricular [INAUDIBLE] device thrombosis. This has been reported. A trend has been increased around 2012, and this is a direct consequence of provider, provider changing recommendations for these patients, because still the adverse event profile was unacceptable in regards to some complication with these devices.

The Intermacs registry has confirmed, which is a large registry in the US, that this was a significant problem. And this led to this PREVENT trial, which I was fortunate enough to be the representative of, where 30 centers across the country went back to basics and looked at surgical medical recommendations that were important for providing better outcomes, specifically in this trial, pump thrombosis at three months with the HeartMate II device.

So surgeons agreed on a certain set of surgical recommendation, and cardiology agreed on a set of recommendation from a medical standpoint, meaning going back to bridging patients with heparin onto an INR 2 to 2.5, using 325 aspirin, maintaining adequate speed, and maintaining blood pressure less than 90. Now doing these things has lead to great improvement in outcomes, going from about a 9% rate of pump thrombosis, report in the New England Journal of Medicine paper, back to about 2.9%, which is far more acceptable for patients with these devices.

Finally, the concept of HeartMate III and hemocompatibility has recently been pulled forward. So this concept really looks at the interaction between patient pump blood and looks at the consequences of having clinical adverse events with these pumps, and separates it in three tier, tier one being a mild, perhaps complication related to the hemocompatibility, less than two GI bleed, suspected pump thrombosis, treated medically, non-stroke related neuro event, like delirium, and arterial thromboembolism, not resulting in an organ stroke.

As we move towards the third tier of hemocompatibility, you're looking at really bad interaction between the patient and the pump, meaning pump malfunction, disabling stroke and death. That is related directly to the pump interaction with the blood. And so doing these and scoring patients in regards to their compatibility with the pump is going to improve our understanding of what's the best pump for each of these patients and what are the important factors for these patients and what should be the best pump for them.

So you can see here that when we compare the HeartMate III in the HeartMate II over a period of time, there's important differences in net hemocompatibility score, perhaps reflecting a better interaction of the pump with the patient. And this has been translated to the identification of which pump should be chosen in different risk factors, whether you have an INR greater or less than a certain level, an advanced age. And so this will lead inevitably to our greater understanding of what should be the best pump for patients.

But the true impact of technology is really comparing apples with apples. As you've seen over this presentation, we've presented device and trial comparison between axial and centrifugal pumps. Our field needs to evolve to really compare most recent technology that is comparable with each other. Hence the HeartWare versus the HeartMate III and with the hope with the approval of the HeartMate III as a bridge to transplant and the hope that this will happen in the next few years.

So the revolution in conclusion of LVAD therapy will depend on outcomes and our ability to improve those outcomes with the pump. Outcomes depend on technology, but also on provider and patient factors. Subgroup analysis are needed, but they need to be data driven, and we have to be critical and move past single centers anecdotal type reports. Studies of similar pump technology are much needed.

While the story of MCS has been one of progressive improvement, and we were much closer, that data to date showed that we have work to do, and we can continue to improve. Thinking that we've accomplished the best result we can with this technology will inevitably result in stagnation.

I'd like to thank our adult transplant and VAD cardiologist team, as well as are VAD surgeons and their VAD coordinators that do exceptional work at taking care of these patients on a daily basis. Thank you.