The VAD Journal: *The journal of mechanical assisted circulation and heart failure*

Brano Heart Failure Forum 2021 Conference Proceeding Paper

Highlights of the 2021 Brano Heart Failure Forum

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Citation: Radovancevic R, et al. Highlights of the 2021 Brano Heart Failure Forum. *The VAD Journal*. 2022; 8(1):e20228110. https://doi.org/10.11589/vad/e20228110

Editor-in-Chief: Maya Guglin, University of Indiana

Received: April 21, 2022

Accepted: September 3, 2022

Published Online: October 18, 2022

Funding: None

Competing interests: None

Keywords: heart failure, heart transplantation, cardiology

Abstract

Since 2007, the Branislav “Brano” Radovancevic Heart Failure Forum has been held annually to provide a venue for experts to present and discuss “Innovations and New Treatment Strategies in Heart Failure.” Clinicians and researchers gather yearly in a different Eastern European city to discuss the latest in heart failure diagnostics and therapeutics. The forum was postponed in 2020 due to the COVID-19 pandemic and then resumed in September of 2021 in Graz, Austria. It was attended by over 75 faculty from 13 countries. Due to the ongoing pandemic, 13 presentations were given virtually. Throughout the forum, 17 separate sessions focused on challenges and solutions related to mechanical circulatory support and heart transplantation. In this special issue of *The VAD Journal*, a summary of conference highlights from available presentations is presented.

Failure Management: COVID-19 Effects and Consequences

Advanced Heart Failure Surgical Management: Impact of the COVID Pandemic

Within nine months of COVID-19 being identified in Wuhan, China, the virus spread worldwide, causing more deaths than HIV, malaria, influenza, cholera, and measles combined. At ten months, there were over 40 million cases worldwide. The early reported mortality in heart and lung transplant recipients was 20% - 30%, but more recently, the rate is estimated to be 15%.[1] Vaccinated transplant patients develop antibodies at much lower titers than the general population. Risk factors for death in the transplant population include age > 60 years and three-drug immunosuppression.[1] The major causes of death in transplant patients with COVID-19 are secondary infection, pulmonary failure, and multiple organ failure. The experience of COVID-19 in pediatric patients is very different than in adults. In a study involving pediatric transplant patients, all were screened for COVID-19, and 21% were positive.[2] Of those positive for COVID-19, 55% were asymptomatic, and there was no mortality. The Pediatric Heart Transplant Society confirmed these findings and reported that COVID-19 in pediatric heart transplant patients is relatively benign. Compared to 2019, there was a 20% reduction in the number of left ventricular assist devices (LVADs) implanted in 2020, and this decrease persisted in 2021. LVAD-supported patients are more susceptible to severe COVID-19, with an estimated mortality of 20% - 25%.

COVID-19: Reversal of Inflammation

The timing of inflammation defines the importance and effectiveness of immunosuppression. Early, aggressive immunosuppression during viral replication leads to more severe COVID-19 symptoms. The best time to actively suppress the inflammatory process is once the virus has triggered the inflammatory cascade. Immune checkpoint inhibitors have transformed how cancer is treated by unleashing the immune system. When the immune system is activated, there are regulatory pathways that decrease the state of inflammation. Immune checkpoint inhibitors with dual agents increase the risk of cardiac immune-related adverse events. In an animal model of heart failure, immune checkpoint inhibitors increased mortality.[3] A way to modulate the inflammatory response in this setting is with Cannabis sativa. A pharmaceutical form of cannabidiol (CBD) is being developed from cannabis for its ability to decrease inflammation. CBD reduces cellular hypertrophy in a dose-dependent manner and attenuates heart failure-induced left ventricular (LV) dysfunction. There is now an ongoing trial studying CBD in patients positive for COVID-19 with a prior history or significant risk factors for cardiovascular disease with the hope that this treatment will reduce the inflammatory cascade that occurs in COVID-19.

EUROMACS and COVID-19

During the COVID-19 pandemic, there was a significant decline in heart failure hospitalizations. In the United Kingdom the decline was 27%, and in Germany, it

was 27%. There was an increase in heart failure mortality for hospitalized patients. Withdrawal from guideline-directed medical therapy was associated with increased mortality. Patients with chronic heart failure were more prone to develop acute heart failure, and 40% of cases were de novo. At one center in Germany, there was a sharp increase in the use of Impella devices due to both the pandemic and reimbursement changes. There was no increase in the use of extracorporeal life support (ECLS) or durable LVADs in INTERMACS profile 1 patients. In Germany, there was a decline in the use of durable mechanical circulatory support (MCS,-12%) and heart transplantation (-13%). The EUROMACS database has recorded 74 patients supported by an LVAD with COVID-19. Of these patients, 49 (66%) required hospitalization with 11 cases of acute heart failure. The in-hospital mortality was 28.6% with the most common cause of death being multiple organ failure, respiratory failure, and cerebrovascular events. Thromboembolic risk during LVAD support remains low, even in patients with COVID-19.

Update on Drug Therapy of Heart Failure

The 2021 European Society of Cardiology (ESC) has introduced new guidelines for diagnosing and treating acute and chronic heart failure.[4] The ESC has a new algorithm for the management of heart failure with reduced ejection fraction (HFrEF) that now includes the use of SGLT2 inhibitors. Subsequently, a study has, for the first time, demonstrated the positive effects of empagliflozin on the treatment of heart failure with preserved ejection fraction. There was an improvement in the cumulative incidence of mortality of 21%. Several treatments can be used for the prevention of heart failure. Patients with Stage A heart failure should receive treatment for hypertension and dyslipidemia, stop nicotine and alcohol, and increase exercise. In patients with Stage B structural heart failure, the addition of ACE inhibitors and beta-blocker therapy is recommended. Medications shown to benefit patients with structural heart disease include Enalapril, Ramipril, Simvastatin, and Clopidogrel. Statin therapy has lipid and non-lipid mechanisms for protection against heart failure and is encouraged to be used. RNA-related drugs have many possibilities including vaccines and Patisiran and Inclisiran to help control LDL cholesterol.

Acute Mechanical Circulatory Support – How to Manage During Pandemics

COVID-19 ECMO: What Worked and What Didn’t

The effectiveness of extracorporeal membrane oxygenation (ECMO) was unknown at the start of the COVID-19 pandemic. Historically, the effectiveness of ECMO therapy was approximately 40% for all causes of acute respiratory distress syndrome (ARDS). China's early results on using ECMO for COVID-19 ARDS were dismal.[5] In a study out of France on 83 patients supported with ECMO for COVID-19, 34 (41%) returned home, and 30 (36%) died.[6] The remaining patients

(23%) were still hospitalized.[6] In a study of 40 patients where ECMO was applied early (13.8 days), the survival rate was 73%.[7] At the Oklahoma Shock and ECMO network, 84 patients with COVID-19 ARDS were supported by ECMO. During the pandemic, the acceptance rate for ECMO therapy was about 1 patient in every 12 referrals. Due to limitations in hospital capacity, the inclusion criteria became progressively stricter. A study of 61 patients supported with ECMO in Oklahoma reported that 22 (40%) died on support, 36 (59%) were weaned from support, and 32 (52%) were discharged. No anticoagulation therapy was used in 28 (46%) patients, and 13 (21%) were extubated while on ECMO support. The EOLIA trial entry criteria are widely accepted for COVID-19 patients requiring veno-venous (V-V) ECMO.[8] The survival rate of V-V ECMO in COVID-19 patients is similar to non-COVID-19 patients. The duration of V-V ECMO is longer in COVID-19 compared to non-COVID-19 cases. There were more bleeding complications than strokes in this population. Of the entire population of hospitalized patients with COVID-19, 80% are unvaccinated.

ECMO Anticoagulation Problems in COVID-19 Patients

Many hospitals remain overwhelmed with COVID-19 cases that require ECMO and ventilator support. Early pandemic data demonstrated that patients who develop pulmonary failure with cytokine storm have significant inflammation with the downregulation of lymphocytes.[9] The coagulation system is affected by these changes. A recent report showed that there is a breakdown of endothelial cells from the COVID-19 infection which causes a platelet – von Willebrand factor interaction.[10] In a comparison between patients with COVID-19 and controls, there is a significant increase in fibrinogen and von Willebrand factor antigen with thrombocytopenia and lymphopenia in the infected patients.[11] Coagulation factors are affected by the severity of the COVID-19 infection. The phases of ECMO therapy in patients with COVID-19 begin with an initial inflammatory insult, followed by organ recovery and endothelial healing. There are then secondary ECMO complications, including coagulopathy. In the initial inflammatory phase of COVID-19, there is an increase in fibrinogen, von Willebrand Factor antigen, and D-dimer, and a decrease in platelets and lymphocytes. Endothelial damage in combination with dysregulated primary hemostasis may lead to severe thrombosis in the arterial and venous circulations. Life-threatening complications of this inflammatory effect may include thrombocytopenic thrombosis, cerebral hemorrhage or infarction, cerebral venous sinus thrombosis, or pulmonary embolism. Unusually long ECMO runtimes are associated with COVID-19 respiratory failure which leads to an increase in secondary ECMO complications.

Impella 5.0 as a Bridge to LVAD Therapy

Recent guidelines have established short-term MCS to be indicated for patients with INTERMACS profiles of 1 or 2 as a bridge-to-decision or bridge-to-transplant.[4] The rationale of short-term MCS is to protect the patient from multi-organ failure and reverse cardiogenic shock until a more definitive therapy can be determined. There are different choices of MCS systems, which are determined by the need to

stabilize hemodynamics and reverse shock to maximize the chance for cardiac and end-organ recovery. In an analysis of pressure-volume loops comparing ECMO with Impella (Abiomed) support, ECMO reversed cardiogenic shock. However, ECMO does not unload the LV, whereas Impella devices do. The Impella device provides the most physiologic support to the LV, but the disadvantage is that it can only provide isolated LV support. In patients with reasonable LV function and sufficient oxygenation, isolated LV support is suitable. For those requiring right-sided or pulmonary support, ECMO plus Impella support may be used. The use of the Impella as a bridge-to-decision during acute, decompensated, advanced heart failure is a common approach used today.[12] Use of the Impella with veno-arterial (V-A) ECMO improves survival of patients with cardiogenic shock.[13] The type of short-term MCS should be individualized to the patient's condition while considering LV, right ventricular (RV), and pulmonary function.

LVAD Complications

Upgrading to Impella 5.5: An innovative Technique with Uninterrupted Support

The Impella CP axial flow pump (Abiomed) is inserted percutaneously and can provide up to 3.5 L/min of support under ideal conditions. The Impella 5.5 (Abiomed) is a larger pump inserted through a graft on the axillary artery and can provide up to 5.5 L/min of cardiac support. For some patients requiring a higher level of cardiac output support, the CP device is exchanged for a 5.5 device. The usual approach for the exchange is to pass a 0.18 wire into the LV, turn off the CP device and remove it, advance the 5.5 device over the wire, remove the wire, and start the pump. During this exchange procedure, there is a period of no support, which some patients do not tolerate well. A technique for uninterrupted support involves passing the Impella 5.5 under fluoroscopic guidance into the LV while the CP device is still functioning. After the position of the 5.5 is confirmed, the wire is removed, and support is transitioned from the CP to the 5.5. Crossing the aortic valve with the wire is easier when the CP is in place and functioning. Hemodynamic instability is avoided during the exchange, and there have not been procedural complications.

HVAD Exchange to HeartMate 3? Pro/Con

The Heartware Ventircular Assist Device (HVAD, Medtronic) has had more Food and Drug Administration recalls than any other device in history. In the MOMENTUM trial, the survival rate at 24 months was 78% for the HeartMate 3 (HM3) compared to 56% for the HeartMate II (HMII).[14] In the CLEAR LVAD study, the HM3 survival rate at 12 months was 85% while the survival for all other LVADs, mostly HVAD, was only 73%.[15] However, in a study comparing short-term outcomes between those supported by the HM3 and HVAD, there was no difference in survival at 3 months, but there were fewer complications in the HM3

patients.[16] During a median follow-up of 15.3 months (range: 0-30 months), 23 (29.1%) and 19 (24.1%) patients died in the HVAD and HM3 groups, respectively. A systematic review of LVAD exchange showed that there are serious complications including RV failure, renal failure, and death.[17] The study also observed that following device exchange, the HM3 is associated with a lower risk of stroke and higher survival than the HVAD. The 30-day mortality following exchange is approximately 10%. In addition, there is a risk of right heart failure (RHF). The reported survival difference after 3-6 months is 5%.

Cardiorenal Syndrome Treatment with Assist Devices: Second Heart Assist Device

Numerous factors play a significant role in cardiorenal syndrome. The most common factor is acute and chronic hemodynamic compromise that is manifested by low cardiac output and blood pressure causing kidney function to deteriorate over time. Non-hemodynamic factors include neural, an imbalance of oxygen and nitric oxide production, humoral, and inflammatory. There have been more than 24 failed drug clinical trials for treating congestive heart failure and cardiorenal syndrome. There is a need for a mechanical solution to treat this problem. There are a variety of temporary, percutaneous MCS systems available today for the treatment of acute heart failure, but they are not optimal for treating cardiorenal syndrome. There are new MCS devices that are positioned in the descending aorta and designed to increase renal blood flow by increasing aortic flow. The rationale for the placement of these devices in the descending thoracic aorta is that they avoid crossing the aortic valve, minimize the risk of stroke, are close to the kidneys, and easy to insert. There is a pressure drop across these pumps, but the amount of blood flow generated in the aorta is unknown.

Challenges in Mechanical Circulatory Support

Insights into Interventricular Interactions in LVAD Patients

The changes in central venous pressure (CVP) and RV hemodynamics in patients supported by the HM3 during a ramp speed test were studied. As the pump speed is increased, the CVP does not change; however, the end-diastolic and end-systolic volumes increase.[18] This data questions the RV and LV interdependence. Interventricular interaction is the influence of LV function on RV function and vice versa. This is often cited in the pathogenesis of post-LVAD RV failure.[19]The components of interventricular interactions are parallel and serial interactions. Because both ventricles share a septum, changes on one side will affect the other side. Testing involves conductance volumetry for pressure-volume analysis in the RV during ramped speed studies. Patterns of interaction are identified by observing changes in the pressure-volume loop with changes in LVAD speed. Changes in pump speed do not change the pressure-volume loop in the RV in most patients; however, other patients show some diastolic pressure interaction. RV systolic interactions are observed in a few patients. Interventricular interactions

manifest heterogeneously. Systolic interactions result in diminished RV systolic function. Diastolic interactions render the RV more compliant and improve function. The balance between these opposing forces and the net effect of interventricular interactions is also variable and patient-specific.

Temporary MCS in Right Heart Failure

The Impella RP device is inserted through the right femoral vein and pumps 2-4 L/min of blood from the right heart to the pulmonary artery. Patients must be immobilized as the right femoral vein is required for insertion. A surgical right ventricular assist device (RVAD) such as Rotoflow, TandemHeart, or CentriMag provides high flow and is inexpensive, and the pulmonary valve is protected. The disadvantages of this type of support are the requirement for an external graft and LVAD explantation and heart transplantation are more difficult. The TandemHeart can be used with a dual cannula technique with the inflow positioned in the right atrium and the outflow in the pulmonary artery. The advantages are that ECMO may be used, and it is inserted percutaneously; however, venous access is required, and the pulmonary valve may be distorted. The Protek Duo, a single dual lumen cannula inserted through the internal jugular vein, may be used with Rotoflow, TandemHeart, or CentriMag pumps and can provide 2-4 L/m of support. This cannula is inserted percutaneously, patients can be mobile, and ECMO can be used, but the right internal jugular vein is required for insertion. Right heart support can also be provided using V-A ECMO. A RHF treatment algorithm gives guidance on the diagnosis of RV failure and the selection of the various methods of support.[20] Use of RVAD support prophylactically with LVAD implantation is important to prevent acute decompensation.

Late Right Heart Failure

The hydraulic impedance of the RV is less than the LV, and the pressure is lower with a continuous decrease.[21] The RV volume and ejection fraction are sensitive to acute changes in afterload. RV function is dependent on LV function because the LV serves as an anchor to the RV.[22] The RV is coupled to a low hydraulic impedance with volumes and ejection sensitized to changes in afterload. RV function is uncoupled when RV function is less than its load. RV output and generation of RV pressure are dependent on LV function. Interventricular interdependence is when the volume and pressure loading of one ventricle impacts the other. LV unloading de-pressurizes the LV, and depending on the Starling point, LV function could decrease or increase. LV unloading may de-pressurize the RV and improve its function. The unpredictable nature of LVAD implantation indicates that the post-implant RV function is determined by pre-implant conditions. The RV has a tremendous capacity to recover function. Consequently, if the RV needs a lot of support after LVAD implantation, the outcome is usually poor. Ten percent of patients with LVADs will develop late RHF. For patients with late RHF, adverse events such as gastrointestinal bleeding and stroke are increased.

Prediction of Right Heart Failure in LVAD Patients

RHF is a frequent post-LVAD implantation complication that contributes to early morbidity and mortality. Prediction and recognition of RHF can help identify high-risk patients, improve patient selection, allow timely intervention, and improve outcomes. Most RHF prediction scores have been derived from small populations and heterogenous cohorts and were done in the earlier generation LVADs. Although prediction models have strong performance in study cohorts, they only have modest performance in general cohorts. Predicting RHF following LVAD implantation is difficult due to the complex and heterogeneous nature of post-LVAD RHF. Novel machine learning models may improve prediction in the future. The EUROMACS-RHF risk score is a simple bedside prediction score that outperforms other known models.[23] Accurate RHF prediction may help to optimize perioperative treatment strategies. Future studies on RHF prediction should determine if these models will improve survival and shorten ICU stays. Better RHF prediction can improve patient selection and shared decision making, more intensive RHF treatment pre-LVAD, guide preemptive use of RVADs, and alternative surgical approaches.

Treatment of Biventricular Failure

For patients with anatomic abnormalities or a high risk of RV or biventricular failure, implantation with a total artificial heart (TAH) or biventricular support (BiVAD) is an acceptable option. The TAH is indicated in patients with clinical conditions or anatomical factors unsuitable for LVAD support. Most of these patients have an INTERMACS profile of 1 or 2, whereas heart transplant recipients typically have an INTERMACS profile of 3 or greater. There are several indications for BiVAD support; however, most patients who receive the support have advanced heart failure and cannot undergo a transplant procedure. Transplant ineligibility diagnoses include cardiac tumors, severe giant cell myocarditis, primary graft failure, and failing Fontan. Thus, TAH with cardiectomy and BiVAD with preservation of the natural heart are alternatives for this subset of patients. BiVAD options include implantation with two VADs, with the preferred implant at the RV or right atrium. Of note, BiVAD support with both HMII and HM3 is off-label. The SynCardia TAH is the only approved device for long-term BiVAD support. Survival in staged BiVAD support is poor and should be avoided. The timing for the implantation of a TAH or BiVAD is crucial and should be as soon as possible. Successful bridge to transplant occurs in approximately 50% of patients supported by the SynCardia TAH, and post-transplant survival is comparable to those with BiVAD support.

Challenges in Heart Failure Interventions

Cardiac Resynchronization Therapy in Heart Failure

Cardiac resynchronization therapy (CRT) is an established therapy for heart failure patients, especially those with left bundle branch block. Despite regional differences, CRT is widely available and should be strictly incorporated into the management of heart failure to reduce the need for more advanced, less available therapies, such as heart transplantation and MCS. The response rate to CRT could be improved by better patient selection and procedural guidance. There is a lack of evidence demonstrating the efficacy of a CRT upgrade; however, the results of a large, randomized study (Budapest-CRT) will be published next year.[24,25] Individual risk stratification for predicting the long-term outcome of CRT is essential. State-of-the-art machine learning methods may help answer the many questions regarding the use of CRT.[26]

Percutaneous Options for Tricuspid and Pulmonic Valves

Tricuspid annular dilation results in poor coaptation of the valve and severe tricuspid regurgitation. The 2020 ACC/AHA guidelines for managing patients with valvular heart disease provide very little information on treating tricuspid valve abnormalities.[27] Valvular heart disease is classified as A, B, C, or D based on symptoms, anatomy, and severity of valve dysfunction. Symptomatic, isolated tricuspid regurgitation may be treated with surgical intervention to reduce symptoms, prevent right heart dysfunction and end-organ damage, and reduce recurrent hospitalizations. There is little published information on the surgical treatment of isolated, severe tricuspid regurgitation. Echocardiographic evaluation is used to assess the severity of valvular dysfunction and for candidate selection for percutaneous treatment of valve dysfunction. Because the anatomy is heterogeneous in these patients, various devices may be applied. Device selection is based on the etiologic mechanism involved in tricuspid regurgitation and the specific anatomic features. The percutaneous option includes procedures for coaptation, annuloplasty, and transcatheter valves. The Melody Transcatheter Pulmonary Valve (Medtronic) is a stented device that can be placed to dilate the pulmonary valve in cases of severe stenosis. Edwards Lifesciences' Sapien valves can be implanted in the RV outflow tract to treat pulmonary valve abnormalities.

Potential Role of Smart Materials in Heart Failure Surgery

The alternatives to heart transplantation include biological (cell therapy and tissue engineering) and mechanical (assist devices and polymers) options. The biological alternatives have not advanced much in recent years; however, MCS has made significant progress. Although, there are remaining challenges with MCS. The ideal mechanical assist device would be pulsatile and has no blood-contacting surfaces. Existing cardiac compression devices have the disadvantage of being pneumatically powered. A novel concept is the application of a polymer that contracts with electrical stimulation and could be placed on a portion of the heart or entirely around the heart.[28] The biological surfaces and pulsatility can be

preserved using electrically contractile polymers. Unfortunately, the electrical efficacy of high-power polymers results in temperatures too high to be used with the heart. Coating the polymer with silicone helps to reduce this heat. Experiments on sheep hearts have demonstrated that high heart rates and pressure as high as 140 mmHg can be achieved. Another novel approach uses carbon nanotubes that can generate electricity when stretched mechanically. Electrical stimulation can cause carbon nanotubes to contract, which has the potential to charge batteries and store power. Thus, it could be used as a pacemaker.

Hot Topics in Heart Transplantation

Long-term Survival after Heart Transplant: Quality of Life

Quality of life (QOL) has been defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient."[29] Data from the International Society of Heart Lung Transplantation show a steady improvement in survival after a heart transplant, and survivors at 5 to 10 years have a QOL that is positive and stable. However, evaluating QOL is complex and requires evaluation of multiple domains. A psychosocial outcomes workgroup of the Nursing and Social Sciences Council established recommendations for assessing QOL following a heart transplant.[30] The numerous domains that contribute to QOL are the transplant, physical functioning, psychological, behavioral, and social. A multi-center study of 555 patients assessing multiple domains out to ten years post-transplant showed very good QOL.[29] Some of the predictors of a worse QOL are depression, fatigue, dermatologic distress, hopelessness, coronary artery vasculopathy (CAV), degree of family stress, transplant event, and uncertainty. QOL is important for transplant recipients, their friends and family, and their healthcare providers. Although QOL has been suggested as a performance metric following transplantation, the complexity and resulting data burden limit its feasibility. Interventions to enhance predictors of good QOL and minimize the effects of factors that decrease QOL are crucial to improving post-transplant QOL.

Clinicopathological Correlates of Early and Late Complications Following Cardiac Transplantation

This study aimed to correlate clinical and pathological findings in patients with a complicated or truncated course leading to reintervention or death following orthotopic heart transplantation. The study included patients treated for heart failure at a single institution between October 2012 and July 2021. The study cohort comprised 51 patients with short-term or long-term complications and a truncated course. Patients were allocated to one of three groups based upon their time from transplant to end-point (death/re-transplant). Group 1 (< 30 days) had 12 patients; Group 2 (30 days to 1 year) had 13; and Group 3 (> 1 year) had 26. Pathologic findings from LV cores, explanted native hearts, post-transplant endomyocardial biopsies and explanted hearts at autopsy were reviewed. The study's results documented three distinct clinicopathological patterns related to the

duration of the post-transplant course. A fatal outcome at < 30 days is characterized clinically by early primary graft dysfunction and is associated with endomyocardial biopsy evidence of acute ischemic damage without acute cellular rejection (ACR) or antibody-mediated rejection (AMR). The fatal outcome between 30 days and 1 year is characterized by graft dysfunction with evidence of ischemic damage often combined with ACR and AMR. Fatal outcomes after 1 year are often due to non-cardiac causes; however, some patients have a combination of graft dysfunction.

Heart Transplantation Is and Will Be the Gold Standard

The current standard therapies for HFrEF are beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, devices (ICD, others), and sodium-glucose cotransporter-2 inhibitors. Part of this therapy regimen can improve QOL to a point. The treatment modalities for end-stage HFrEF are MCS, heart transplantation, and compassionate end-of-life care. MCS requires a percutaneous connection, external power and control, and no submersion in water. Heart transplantation requires medications, regular medical contact, and an increased risk of cancer and infection. Compassionate care varies in regimen but would involve stopping all devices and medications. The QOL following transplantation is mostly very good, which is documented by the ISHLT through a survey of patients after transplantation. The functional status of heart transplant recipients measured by the Karnofsky score shows excellent results out to 5-years after transplant. Interestingly, self-reported employment status after transplant indicates that many patients are not working. However, in large part because of survival, heart transplantation remains the gold standard for the treatment of end-stage heart failure.

Dr. David O. Taylor Memorial Lecture

Man of Unprecedented Intelligence, Humility, and Kindness

David Taylor was born May 22, 1959, and was raised in Artesia, New Mexico. David matriculated from Baylor University to the University of New Mexico School of Medicine. He completed Internal Medicine Residency, Cardiology Fellowship, and Heart Failure Transplant Fellowships at the Medical College of Virginia (MCV). At MCV, David was under the mentorship of Dr. Michael Hess who inspired him to pursue a career in heart failure and transplantation. David's career in heart failure began in 1991 at the age of 34 years when he became the Medical Director of the heart transplant program at the VA Medical Center in Salt Lake City. At the age of 42, David achieved the appointment of Professor of Medicine at the University of Utah. In 2001 David moved to the Cleveland Clinic and was the Director of the Heart Failure/Transplantation Fellowship Program from 2004 to 2017. David was frequently honored as the Teacher of the Year at the Cleveland Clinic. His academic achievements include over 200 published research papers, review articles and book chapters, and numerous lectures around the world. In addition to

his clinical and academic responsibilities, David devoted much of his time to the community and served at the ISHLT president from 2012 to 2013. After his Presidency at ISHLT his commitment to the society continued with activities on multiple committees, task forces and the *Journal of Heart Lung Transplantation*. In 2021, the ISHLT awarded Dr. Taylor with its highest honor, the Lifetime Achievement Award. David was a Master of Work-life balance and was profoundly dedicated to his family. David participated in many of the Brano Heart Failure Forum meetings and was a very active presenter and discussant. Thousands of patients are indebted to David for saving their lives and he will be remembered as a legendary educator, valued mentor, skilled physician, and amazing colleague.

The Cardiac iBox

There is an unmet need for a predictive model to better identify risks and outcomes. The Cardiac iBox system has the potential for risk stratification by machine learning and algorithmic decision-making. Algorithms can synthesize multiple variables and quantify risk. System inputs include noninvasive biomarkers, gene expression, histology, clinical presentation, and immunology. Advanced statistical analysis includes collinearities, performance, discrimination, calibration, validation, competing risk, and adaptability which culminate into diagnostic risk prediction. The study “Identification and Characterization of Trajectories of Cardiac Allograft Vasculopathy after Heart Transplantation” used multiple donor and recipient characteristics from 1301 transplanted patients using precision medicine to predict outcomes.[31] Analysis of 1-year data was used to predict outcomes at 5 and 10 years after transplant. The statistical analysis used was a latent class mixed model (LCMM) with an unsupervised method adapted to repeated measurements allowing the detection of underlying groups in longitudinal data. Statistical parameters are tested to obtain the best profiles of CAV trajectories. LCMM associates logistic regression and a mixed model. Patients are given likelihoods of belonging to latent classes. Baseline characteristics showed that the average donor age in the United States was significantly less than in Europe, which explains why there was less donor-transmitted disease in US patients. Multiple studies have shown that older donors have more CAV. Of the 4 trajectories of CAV, latent class 1 will do well and doesn’t need annual coronary angiograms, whereas latent class 4 has some CAV at 1-year and have a poor trajectory that should lead to adjustments in therapy. A higher percentage of patients with younger donors are in latent class 1 vs. latent class 4 having significantly older donors. Multivariate analysis showed that there are donor, recipient, and immunologic risk factors for developing CAV. There is now an online calculator that will provide a personalized prediction of CAV trajectory. Future use of the Cardiac iBox includes donor selection, response to treatment, and treatment recommendations.

Challenges in Heart Transplantation

Antibody-Mediated Rejection: What's new?

Current therapeutic developments include the management of pre-sensitized patients before transplant and treating AMR. There are several off-label drugs now being used to treat these patients. Eculizumab, imlifidase, and interleukin-6 (IL-6) inhibitors are medications where there is now data to demonstrate efficacy. The safety and effectiveness of bortezomib are suboptimal for desensitization and treatment. In a small single-center study, eculizumab was shown to prevent AMR after a heart transplant with a lower incidence of biopsy-proven AMR.[32] However, there was no difference in study outcomes or survival.[32] Imlifidase is a new drug approved for kidney transplantation that has shown promise in a few small studies. So far, eculizumab and imflidase appear to provide a good risk/benefit ratio for desensitization. Anti-IL-6 therapies are promising for AMR treatment. The treatment of AMR with cytokine IL-6 blockade was developed as an autoimmune treatment and used in kidney transplantation.[33] Therapeutic strategies are lacking, although repurposing antibodies developed for other diseases provides encouraging results. Despite these advancements, AMR remains a clinical challenge after heart transplantation.

Flow Cytometric Crossmatch Assay to Identify Recipient IgG Subtype Antibodies

Human immunoglobulin G (IgG) is composed of two heavy and light chains linked together by interchain disulfide bonds, which are responsible for forming three-dimensional loops and the compact, domain-like structure of the molecule. Complement activation is triggered by binding immunoglobulin. The hinge region of IgG1 and IgG3 are very flexible and can efficiently bind complement, whereas IgG2 and IgG4 are less flexible and bind complement less efficiently. Single antigen bead testing is the gold standard for identifying donor-specific antibodies, and mean fluorescence intensity is the report generated. Importantly, all donor-specific antibodies are not equal in terms of risk. A standard flow crossmatch in the presence of donor-specific antibodies will be positive because it tests the reaction of IgG 1-4 as a group. It is uncertain if knowing the IgG subclass or binding complement ability is clinically useful. Indeed, transplants can be done safely despite a positive flow crossmatch if the offending IgG is 2 or 4, not 1 or 3. The New Jersey Organ and Tissue Sharing Network Lab developed a patented flow crossmatch methodology allowing the immunologist to determine the subclass of the donor-specific antibody. The information from this crossmatch can be correlated with a CD3 antibody assessment and provide a real-time picture of the risk of acute and accelerated AMR. With this testing, it is hypothesized that approximately 380 more heart transplants could be done nationally.

Monitoring for Acute Rejection: is there a role left for the heart biopsy?

In 2006, it was reported that over 50% of transplant centers were performing biopsy surveillance greater than ten years after the transplant.[34] Genomic-based rejection monitoring has since been developed. The proportion of positive all-cause biopsies with ACR dating back to 1997 has been studied. The yield of positive biopsies was much higher for clinically driven biopsies versus routine surveillance biopsies. More recent studies have shown that the proportion of treatable ACR by biopsy is less than 2%.[31] AMR is prevalent, difficult to treat, and can lead to graft dysfunction and allograft vasculopathy. There is a strong correlation between the presence of pathologic AMR and cardiovascular mortality.[35] De-novo, class II donor-specific antibodies predict AMR and graft loss and can be used to risk stratify patients. The current role of endomyocardial biopsy is to evaluate graft dysfunction to differentiate causes, guide the intensity of immunotherapy, and exclude rejection in patients with symptoms of graft dysfunction or abnormal noninvasive testing. Routine surveillance heart biopsies in asymptomatic patients are being gradually phased out in favor of clinical and non-invasive surveillance using biomarkers such as donor-derived cell-free DNA.

Noninvasive Surveillance After Heart Transplantation

Much progress has been made in the quest for noninvasive ways to assess graft health after transplant. There is now better outcomes management with fewer and better-targeted biopsies and fewer procedural complications. In the United States, there are two assays used for noninvasive surveillance of acute rejection: gene expression profiling (GEP, AlloMap) for determining immune activation and donor-derived cell-free DNA (dd-cfDNA) for assessing graft injury (AlloSure). Gene expression signatures of immune activation and leukocyte trafficking are detectable and can be compared to the rejection status of the allograft. A test was developed from 11 genes that had differentially expressed profiles in the setting of acute rejection.[36] An algorithm can quantify the gene expression and produce a classifier score of 1 to 40, with the higher numbers associated with acute rejection. In the IMAGE study, the primary outcome was not different between groups monitored for rejection using biopsy or GEP.[37] The limitations of the AlloMap GEP testing include a low positive predictive value and a lack of validation for AMR; it is also affected by several clinical factors. AlloSure detects both ACR and AMR; it is a valuable indicator of acute rejection and a sensitive marker of graft injury.[38] The dd-cfDNA levels may be significantly elevated up to 5 months before the rejection event.[39] AlloMap GEP test can be used at 55 days post-transplant, and AlloSure can be used starting at one month. Many biopsies have been eliminated with safe and effective heart transplant surveillance.

Challenges in Transplantation and Heart Failure Management

Heart Transplantation: Best Outcomes without Losing Patients on the Waiting List

A paradox in heart transplantation in the United States is that the donor allocation is based solely on the risk of waitlist mortality. Still, the Scientific Registry of Transplant Recipients (SRTR) assessment of results is primarily based on post-transplant survival. The biggest change in donor characteristics in recent years is the number of donors experiencing anoxic brain death from a drug overdose, which is now almost 25% of all donors. The number of donors has increased for those with a history of cocaine and other drug use, diabetes, and hypertension. The use of donors with an LVEF <50% has decreased. There has been a steady decline in waitlist mortality for all age groups, with those over 65 years having the highest mortality.[40] The donor allocation system in the United States changed in 2018, resulting in most transplants being status 1 and 2 patients. Recent data from the ISHLT shows that donors over 50 years and ischemic time over 4 hours are associated with the lowest survival rates at one year. Recent changes in transplant recipient characteristics include increasing age and body mass index—both factors are associated with higher 1-year mortality risk.[41] A recent publication presents information that questions the currently used modeling for transplant outcomes.[42] In the United States, perhaps the focus should be on post-transplant survival and not waitlist mortality.

Frailty and Patient Selection for LVAD or Transplant

Frailty is a complex state of increased vulnerability to physiologic stress distinct from aging, comorbidity, and disability. Individuals develop a state of physical decline that is out of proportion to their chronic illness. While there are more than 20 tools and assessments to evaluate frailty, no gold standard assessment exists.

A measure of frailty for advanced heart failure is needed. Such a tool should be validated and measure typical features of frailty. Importantly, it should assist in distinguishing heart failure-related debility vs. frailty-related debility. The measure should help to predict clinical outcomes after LVAD implantation and determine if the patient should undergo rehabilitation activities before implantation. Also, the metric should be responsive to LVAD-reversible frailty. There are numerous overlapping symptoms of frailty and heart failure, and these should be identified.

The Fried criteria for assessing frailty is extensively validated and includes unintentional weight loss, exhaustion, low physical activity, gait speed, and hand grip strength. In a study of patients with LVADs, the Fried criteria did not predict survival; however, exhaustion, inactivity, and grip strength did predict >30-day hospitalization. The Essential Frailty Toolset uses multiple measures of frailty and is an excellent predictor of morbidity and mortality in cardiac surgical patients.[43] While there is a lack of consensus on which assessment tools to use, working groups are paying increased attention to the importance of frailty.

Cardiac Xenotransplantation Update

The main problem in allotransplantation is the growing shortage of acceptable donors. Multiple measures can be taken to enhance the number of donors, such as policy changes from opt in to opt out, accepting sicker and older donors, expanding the donor pool to include donations after circulatory death, and using novel preservation techniques to increase the ex-vivo time of donor hearts - but none have had a significant impact. Genetically modifying suitable animal organs for transplantation in humans (xenotransplantation) to mitigate the organ shortage problem is the core idea behind xenotransplantation. A recent breakthrough in xenotransplantation occurred in 2016, where an immunological cardiac xenograft was transplanted heterotopically (n=5) from pigs to baboons with a survival rate of up to 945 days.[44] With immunosuppressive therapy, there were no signs of rejection in these animals. In 2018, five orthotopic (ie, life-supporting) porcine cardiac xenografts were transplanted with the same genetic modification into baboons. These baboons survived consistently up to 195 days with life supporting porcine hearts.[45] With adjusted immunosuppression, there were no signs of rejection. Three fundamental changes to existing protocols are believed to be key to this success. Firstly, to avoid primary xenograft dysfunction, which was previously observed in up to 60% of porcine cardiac xenografts, a novel perfusion system using continuous oxygenated hyperoncotic cold cardioplegic solution with red blood cells, albumin, nutrition, and hormones was used, thus able to avoid primary xenograft dysfunction. Then it was necessary to prevent cardiac xenograft overgrowth, which was achieved with m-TOR pathway inhibitor rapamycin. Zoonotic infections present another challenge, as pathogen-free pigs must be used as donors - specifically free of PERV-C and porcine cytomegalovirus. Current research includes expanded genetic modification, adapted immunosuppression, and prevention of zoonotic infections, which will be validated in studies with 6-month survival follow-up. Clinical trials may then be undertaken in patients needing a re-transplant who are highly sensitized, older, have an allotransplantation contraindication, or have a VAD contraindication.

References:

1. Genuardi MV, Moss N, Najjar SS, et al. Coronavirus disease 2019 in heart transplant recipients: Risk factors, immunosuppression, and outcomes. *J Heart Lung Transplant*. Sep 2021;40(9):926-935. doi:10.1016/j.healun.2021.05.006

2. Bock MJ, Kuhn MA, Chinnock RE. COVID-19 diagnosis and testing in pediatric heart transplant recipients. *J Heart Lung Transplant*. Sep 2021;40(9):897-899. doi:10.1016/j.healun.2021.06.009

3. Rubio-Infante N, Ramirez-Flores YA, Castillo EC, Lozano O, Garcia-Rivas G, Torre-Amione G. Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis. *Eur J Heart Fail*. Oct 2021;23(10):1739-1747. doi:10.1002/ejhf.2289

4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. Sep 21 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368

5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. May 2020;8(5):475-481. doi:10.1016/S2213-2600(20)30079-5

6. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. Nov 2020;8(11):1121-1131. doi:10.1016/S2213-2600(20)30328-3

7. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure. *JAMA Surg*. Oct 1 2020;155(10):990-992. doi:10.1001/jamasurg.2020.3950

8. Combes A, Brechot N, Luyt CE, Schmidt M. Indications for extracorporeal support: why do we need the results of the EOLIA trial? *Med Klin Intensivmed Notfmed*. Feb 2018;113(Suppl 1):21-25. Indikationen fur die extrakorporale Unterstutzung: Warum brauchen wir die Ergebnisse der EOLIA-Studie? doi:10.1007/s00063-017-0371-0

9. Lingeswaran M, Goyal T, Ghosh R, et al. Inflammation, Immunity and Immunogenetics in COVID-19: A Narrative Review. *Indian J Clin Biochem*. Jul 2020;35(3):260-273. doi:10.1007/s12291-020-00897-3

10. Choudhary S, Sharma K, Singh PK. Von Willebrand factor: A key glycoprotein involved in thrombo-inflammatory complications of COVID-19. *Chem Biol Interact*. Oct 1 2021;348:109657. doi:10.1016/j.cbi.2021.109657

11. Al Otair H, AlSaleh K, AlQahtany FS, et al. The Level of vWF Antigen and Coagulation Markers in Hospitalized Patients with Covid-19. *J Blood Med*. 2021;12:809-817. doi:10.2147/JBM.S318940

12. Hall SA, Uriel N, Carey SA, et al. Use of a percutaneous temporary circulatory support device as a bridge to decision during acute decompensation of advanced heart failure. *J Heart Lung Transplant*. Jan 2018;37(1):100-106. doi:10.1016/j.healun.2017.09.020

13. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella((R)) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail*. Mar 2017;19(3):404-412. doi:10.1002/ejhf.668

14. Mehra MR, Goldstein DJ, Uriel N, et al. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N Engl J Med*. Apr 12 2018;378(15):1386-1395. doi:10.1056/NEJMoa1800866

15. Pagani FD, Mehra MR, Cowger JA, et al. Clinical outcomes and healthcare expenditures in the real world with left ventricular assist devices - The CLEAR-LVAD study. *J Heart Lung Transplant*. May 2021;40(5):323-333. doi:10.1016/j.healun.2021.02.010

16. Schramm R, Zittermann A, Morshuis M, et al. Comparing short-term outcome after implantation of the HeartWare(R) HVAD(R) and the Abbott(R) HeartMate 3(R). *ESC Heart Fail*. Jun 2020;7(3):908-914. doi:10.1002/ehf2.12649

17. Austin MA, Maynes EJ, Gadda MN, et al. Continuous-flow LVAD exchange to a different pump model: Systematic review and meta-analysis of the outcomes. *Artif Organs*. Jul 2021;45(7):696-705. doi:10.1111/aor.13893

18. Uriel N, Medvedofsky D, Imamura T, et al. Echocardiographic Changes in Patients Implanted With a Fully Magnetically Levitated Left Ventricular Assist Device (Heartmate 3). *J Card Fail*. Jan 2019;25(1):36-43. doi:10.1016/j.cardfail.2018.11.015

19. Brener MI, Hamid NB, Fried JA, et al. Right Ventricular Pressure-Volume Analysis During Left Ventricular Assist Device Speed Optimization Studies: Insights Into Interventricular Interactions and Right Ventricular Failure. *J Card Fail*. Sep 2021;27(9):991-1001. doi:10.1016/j.cardfail.2021.04.019

20. Kapur NK, Esposito ML, Bader Y, et al. Mechanical Circulatory Support Devices for Acute Right Ventricular Failure. *Circulation*. Jul 18 2017;136(3):314-326. doi:10.1161/CIRCULATIONAHA.116.025290

21. Redington AN, Gray HH, Hodson ME, Rigby ML, Oldershaw PJ. Characterisation of the normal right ventricular pressure-volume relation by biplane angiography and simultaneous micromanometer pressure measurements. *Br Heart J*. Jan 1988;59(1):23-30. doi:10.1136/hrt.59.1.23

22. Zuk K, Gahl B, Susac M, et al. Mid-term mechanical circulatory support: comparison of single-centre data with the EUROMACS registry. *Eur J Cardiothorac Surg*. Jan 2017;51(1):127-134. doi:10.1093/ejcts/ezw256

23. Soliman OII, Akin S, Muslem R, et al. Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score. *Circulation*. Feb 27 2018;137(9):891-906. doi:10.1161/CIRCULATIONAHA.117.030543

24. Merkely B, Geller L, Zima E, et al. Baseline clinical characteristics of heart failure patients with reduced ejection fraction enrolled in the BUDAPEST-CRT Upgrade trial. *Eur J Heart Fail*. Sep 2022;24(9):1652-1661. doi:10.1002/ejhf.2609

25. Merkely B, Kosztin A, Roka A, et al. Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial. *Europace*. Sep 1 2017;19(9):1549-1555. doi:10.1093/europace/euw193

26. Tokodi M, Schwertner WR, Kovacs A, et al. Machine learning-based mortality prediction of patients undergoing cardiac resynchronization therapy: the SEMMELWEIS-CRT score. *Eur Heart J*. May 7 2020;41(18):1747-1756. doi:10.1093/eurheartj/ehz902

27. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. Feb 2 2021;143(5):e72-e227. doi:10.1161/CIR.0000000000000923

28. Kongahage D, Ruhparwar A, Foroughi J. Artificial Muscles: High Performance Artificial Muscles to Engineer a Ventricular Cardiac Assist Device and Future Perspectives of a Cardiac Sleeve. *Advanced Materials Technologies*. 2021;6(5):2170025. doi:https://doi.org/10.1002/admt.202170025

29. Psychosocial Outcomes Workgroup of the N, Social Sciences Council of the International Society for H, Lung T, et al. Report of the Psychosocial Outcomes Workgroup of the Nursing and Social Sciences Council of the International Society for Heart and Lung Transplantation: present status of research on psychosocial outcomes in cardiothoracic transplantation: review and recommendations for the field. *J Heart Lung Transplant*. Jun 2006;25(6):716-25. doi:10.1016/j.healun.2006.02.005

30. Grady KL, Naftel DC, Kobashigawa J, et al. Patterns and predictors of quality of life at 5 to 10 years after heart transplantation. *J Heart Lung Transplant*. May 2007;26(5):535-43. doi:10.1016/j.healun.2007.01.042

31. Loupy A, Coutance G, Bonnet G, et al. Identification and Characterization of Trajectories of Cardiac Allograft Vasculopathy After Heart Transplantation: A Population-Based Study. *Circulation*. Jun 16 2020;141(24):1954-1967. doi:10.1161/CIRCULATIONAHA.119.044924

32. Patel JK, Coutance G, Loupy A, et al. Complement inhibition for prevention of antibody-mediated rejection in immunologically high-risk heart allograft recipients. *Am J Transplant*. Jul 2021;21(7):2479-2488. doi:10.1111/ajt.16420

33. Doberer K, Duerr M, Halloran PF, et al. A Randomized Clinical Trial of Anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection. *J Am Soc Nephrol*. Mar 2021;32(3):708-722. doi:10.1681/ASN.2020071106

34. Stehlik J, Starling RC, Movsesian MA, et al. Utility of long-term surveillance endomyocardial biopsy: a multi-institutional analysis. *J Heart Lung Transplant*. Dec 2006;25(12):1402-9. doi:10.1016/j.healun.2006.10.003

35. Hammond MEH, Revelo MP, Miller DV, et al. ISHLT pathology antibody mediated rejection score correlates with increased risk of cardiovascular mortality: A retrospective validation analysis. *J Heart Lung Transplant*. Mar 2016;35(3):320-325. doi:10.1016/j.healun.2015.10.035

36. Deng MC, Eisen HJ, Mehra MR, et al. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant*. Jan 2006;6(1):150-60. doi:10.1111/j.1600-6143.2005.01175.x

37. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. *N Engl J Med*. May 20 2010;362(20):1890-900. doi:10.1056/NEJMoa0912965

38. Khush KK, Patel J, Pinney S, et al. Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: A prospective multicenter study. *Am J Transplant*. Oct 2019;19(10):2889-2899. doi:10.1111/ajt.15339

39. De Vlaminck I, Valantine HA, Snyder TM, et al. Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection. *Sci Transl Med*. Jun 18 2014;6(241):241ra77. doi:10.1126/scitranslmed.3007803

40. Colvin M, Smith JM, Ahn Y, et al. OPTN/SRTR 2019 Annual Data Report: Heart. *Am J Transplant*. Feb 2021;21 Suppl 2:356-440. doi:10.1111/ajt.16492

41. Khush KK, Hsich E, Potena L, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult heart transplantation report - 2021; Focus on recipient characteristics. *J Heart Lung Transplant*. Oct 2021;40(10):1035-1049. doi:10.1016/j.healun.2021.07.015

42. Dolgner SJ, Nguyen VP, Cowger J, Dardas TF. Accuracy of risk models used for public reporting of heart transplant center performance. *J Heart Lung Transplant*. Dec 2021;40(12):1571-1578. doi:10.1016/j.healun.2021.07.027

43. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *J Am Coll Cardiol*. Aug 8 2017;70(6):689-700. doi:10.1016/j.jacc.2017.06.024

44. Mohiuddin MM, Singh AK, Corcoran PC, et al. Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of GTKO.hCD46.hTBM pig-to-primate cardiac xenograft. *Nat Commun*. Apr 5 2016;7:11138. doi:10.1038/ncomms11138

45. Langin M, Mayr T, Reichart B, et al. Consistent success in life-supporting porcine cardiac xenotransplantation. *Nature*. Dec 2018;564(7736):430-433. doi:10.1038/s41586-018-0765-z