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

**Brano Heart Failure Forum Proceeding Paper**

# Highlights of the 2022 Brano Heart Failure Forum: Part One

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## Abstract

Since 2007, the Branislav “Brano” Radovancevic Heart Failure Forum (BHFF) 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 2022 BHHF forum was held on the 6th thru 8th of September 2022 in Trieste, Italy. It was attended by over 94 faculty from 14 countries. In addition, participation through online streaming was available. Throughout the forum, 17 sessions focused on challenges and solutions related to mechanical circulatory support and heart transplantation. This special issue of *The VAD Journal* presents a summary of conference highlights from available presentations.

# Important Elements of a Successful Extracorporeal Membrane Oxygenation Program

## Extracorporeal Membrane Oxygenation in Primary Graft Dysfunction – How Long?

*Presenter Ruzica Mrkonjic*

The selection of patients for extracorporeal membrane oxygenation (ECMO) support is a critical component of any perfusion program. Teams must evaluate when to start the support, how long to support the patient, and when is the ideal time to wean. The timing of ECMO support is debated. While some programs emphasize prompt timing, others suggest a conservative approach is better (>7 hours). Delaying ECMO support could increase complications; thus, more evidence has been attained for prompt support. Importantly, complications are common with ECMO support. Despite advances over the last ten years, the risk of bleeding remains high.[1] Seminal studies to address the issue have been conducted, and current guidelines have evolved based on the findings.[2] One of the newest technologies is Cytosorb (CytoSorbents Inc.); however, the optimization of its use and true efficacy is unknown. Our institution has recently used the Seraph 1000 Microbind Affinity blood filter, which allows up to a 90% reduction of bloodstream pathogens during a single treatment. We found it a highly effective approach and a possible advancement for septic patients.

## Reducing Gaseous Microemboli

*Presenter Slavko Kulic*

The incidence of cerebral adverse events after cardiac surgery ranges from 1 to 3%.[3] One potential mechanism for developing cognitive deficits is the gaseous micro-emboli (GME) arising from the use of cardiopulmonary bypass support. Arterial line filtration reduces the number and volume of GME entering the systemic circulation.

A new oxygenator design is being developed to enable arterial filters to fit with the oxygenator housing and provide the advantages of low priming volume, high gas exchange, and low-pressure drops. To optimize the design, we are comparing three types of oxygenators at our institution (Terumo $FX_{25}$, Sorin F8, Sorin 8). We are comparing the volume and number of GME by using Gampt $BC_{200}$. We will also compare cognitive dysfunction, platelet number and function, hemoglobin and hematocrit, and other outcomes in 100 enrolled patients. The initial results are promising.

## A Decade of Extracorporeal Membrane Oxygenation

*Presenter Lisa Janowiak*

The use of ECMO has progressively and exponentially increased since its first use in the 1970s. Since 2012, our institution has supported over 1000 patients who required ECMO therapy in a variety of clinical situations, including, but not limited to, postpartum, traumatic injury, elderly, transcatheter aortic valve replacement (TAVR), and COVID-19.[4-7]

In patients with trauma, the ECMO experience is limited and often debated. The ideal candidate is a young patient with a reversible disease process, minimal comorbidities, and good baseline cardiopulmonary function. We found that using veno-venous (V-V) ECMO support in this population is advantageous as the survival-to-discharge rate was 87%. We also found advantages when ECMO was on standby in the catheterization laboratory to be used as a rescue therapy during TAVR procedures.[7]

Most recently, we studied and published our institutional algorithm to assist regional hospitals with ECMO initiation for patients infected with COVID-19 who needed air ambulance transportation for higher levels of care and support.[8] Research like ours is strongly supported by the efforts of the Extracorporeal Life Support Organization (ELSO)'s Registry and our institutional database.

## Foundations of Success for Nursing

*Presenter Marie Clark*

There are many challenges for nursing in the field of ECMO. During the COVID-19 pandemic, many nurses transitioned to travel nursing or left the field altogether due to burnout or post-traumatic stress disorder. Thus, the shortage of nurses was exacerbated. In current times, the training process for nurses must be staged. The process from beginner to proficient requires time and dedicated training with experienced staff that prioritizes teaching. On average, this process takes three to four years. Once proficient, a nurse can deal with various scenarios and severity. To ensure success, perform assessments and reassess as necessary. Try and pair nurses with patients within their scope, and pair beginners with those who can best train and speak to them at their level.

## Organizing Mechanical Circulatory Support: Personnel Requirements

*Presenter Saso Klesnik*

At our institution, a dedicated staff team manages the patients with mechanical circulatory support (MCS) (both acute and durable). The staff works with patients and

includes 24/7 coverage. The group is responsible for in-hospital care and patient education on devices. The team members must be trained in the operating room and cath lab procedures, including room etiquette and sterile techniques. After surgery, the team collects vital pump parameters and monitors patients. They regularly communicate with the multidisciplinary team that is focused on the patient.

Members with graduate training in biomedical engineering and basic knowledge of anatomy and physiology are preferred candidates, as their background can aid in troubleshooting issues with the various support devices. Staff must function under stressful situations and communicate clearly regarding complicated engineering concepts. Importantly, the MCS team does not replace the ventricular assist device coordinator or perfusion team; rather, they support and work in a multidisciplinary fashion.

## Technical Issues in Transmedics Organ Perfusion

*Presenter Andrea Lechiancole*

There are three major types of issues with transmedics organ perfusion. First, donor management requires assessment for contraindications and sets the goal to achieve a high of greater than 25% and a central venous pressure greater than 6 mm Hg. The second type of issue is blood collection. Boluses of inotropes and vasopressors should not be used during blood collection. The third type of issue involves donor heart instrumentation. Aortic and pulmonary artery cannulation must be done carefully to ensure successful outcomes. One must ensure proper alignment of the aorta and inferior vena cava. After perfusion is initiated, left ventricular (LV) function and pulmonary flow are confirmed. Perfusion is often monitored via the lactate level. If lactate begins to increase, one must suspect inadequate perfusion. The pump speed and maintenance solution rate can be modulated if this is detected.

## The Role of Purification in Organ Transplantation

*Presenter Massimo Boffini*

Ex vivo lung perfusion (EVLP) for transplantation can be done via multiple protocols, each with advantages and disadvantages. Primarily, ex-vivo perfusion is used for evaluation; however, it could be used in possible treatments. EVLP ameliorates acute lung injury, reduces ischemia-reperfusion injury, and promotes tissue homeostasis via multiple pathways. Further, this process results in a significant increase in cytokines. The cytokine profile may predict the behavior of the graft; this process is recommended at some centers).[9] If inflammatory cytokines are successfully removed from the perfusate using an adsorber, this process could improve outcomes, especially with

injured grafts.[10] In preclinical studies using the porcine model, transplanted organs that have been filtered have favorable outcomes.[11] In Turin, Italy, an EVLP program completed 55 procedures. Positive reconditioning was higher in the cohort using the Cytosorb technology than the standard protocol (76% versus 65%, respectively).

## Heart Failure Management: COVID-19 Effects and Consequences

### Effect of SARS-CoV-2 on the Cardiovascular System

*Presenter Marco Merlo*

The relationship between cardiovascular (CV) damage and COVID-19 is complex and being studied.[12] Pre-existing cardiac disease and CV risk factors, such as hypertension, have a known prognostic role.[13-15] Of note, a myocardial injury (ie, increased troponin values) is frequent and likely to have a prognostic impact on patients who are infected with SARS-CoV-2. Serial troponin measurements in patients admitted for COVID-19 infections also have prognostic value, signaling an increased mortality risk. The cause of COVID-19-related myocarditis is likely through indirect pathways that include a cytokine storm rather than a direct effect, but this concept remains controversial. The literature is still in development, but no evidence of the viral genome in cardiomyocytes exists. Myocarditis is an uncommon event that should not distract from other possible diagnoses. Finally, no causal link has been found between vaccination and myocarditis. Because of the very low incidence, only a temporal link has been found.[16] The natural history of vaccine-related myocarditis is more benign of CV mortality induced by SARS-CoV-2. Thus, personalized risk balance must weigh age, sex, job, and other risk factors with the risk of cytokine release and myocarditis. Overall, COVID-19 vaccination is recommended to prevent major complications and death.[16]

### Update on Cardiac Resynchronization Therapy in Heart Failure

*Presenter Annamaria Kosztin*

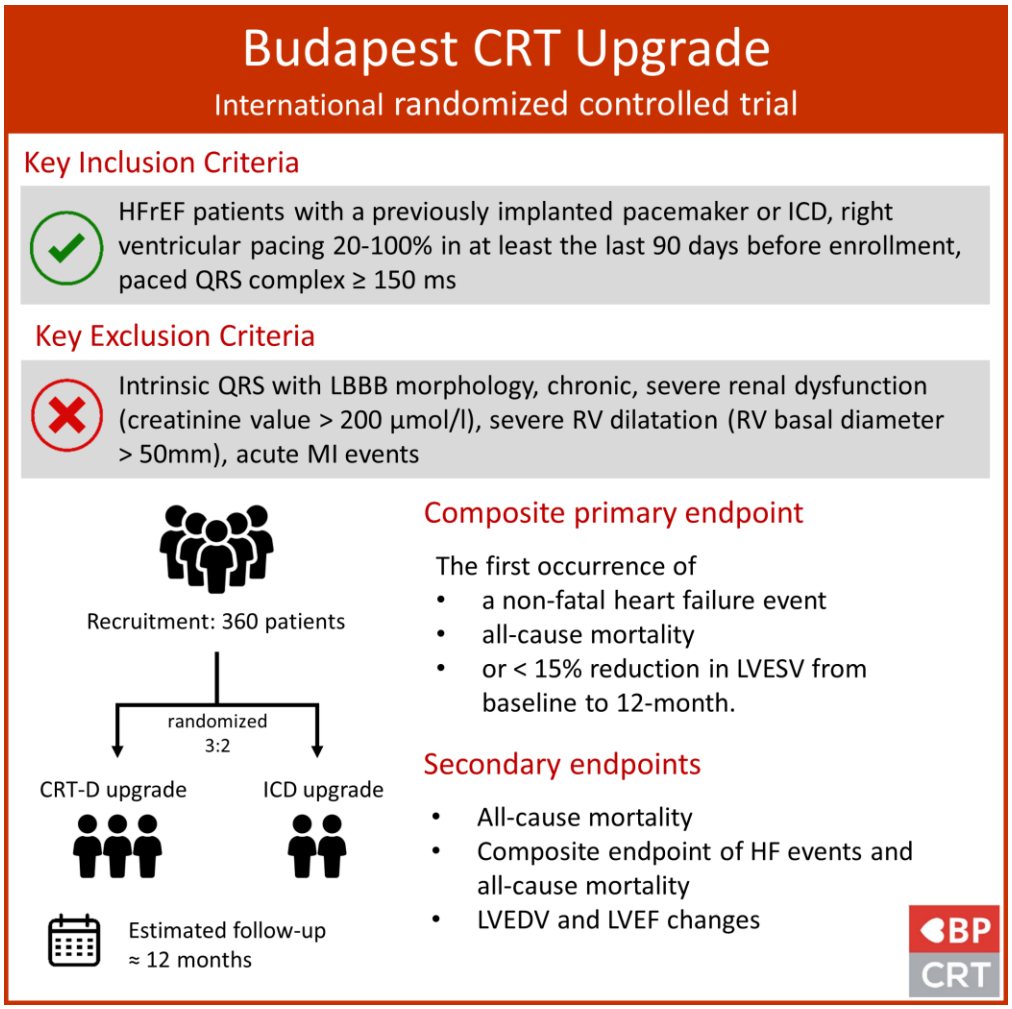
The guidelines for cardiac resynchronization therapy (CRT) were recently updated in 2021.[17] Patients who received an implantable cardioverter defibrillator (ICD) or conventional pacemaker and subsequently developed symptomatic heart failure with a left ventricular ejection fraction (LVEF) ≤35% despite optimized medical therapy and those who have a significant proportion of right ventricular (RV) pacing should be considered for CRT upgrade with a Class IIa, Level B recommendation.[17]

The BLOCK HF trial proved the superiority of biventricular pacing as compared to RV pacing in patients with an LVEF <50% and atrioventricular block.[18] However, no randomized controlled trials (RCTs) provide data for patients with an LVEF <35% and a

high proportion of RV pacing. In this context, the BUDAPEST-CRT Upgrade trial (NCT02270840) is the first aimed at this purpose.[19] While the study's final results have not been reported, the baseline clinical characteristics were recently published.[20] Of note, male patients are over-represented, and a history of atrial fibrillation is present in 56.4% of the patients. Further, almost half of them had a hospitalization in the previous 12 months.[20] This trial highlighted which patients should be followed strictly in everyday clinical practice to perform the CRT upgrade in time.

To decide whether a patient should receive the CRT-D or CRT-P, the patient's baseline characteristics must be carefully considered, and risk assessment must be individualized.[17] Risk stratification uses machine learning methods to create risk scores, such as the SEMMELWEIS-CRT score.[21,22]

Although newer, conduction system pacing techniques (His and LBBA) appear to have similar efficacy to that of CRT. However, this needs to be confirmed with RCTs.[17]



## Allocation of Hospital Resources during the COVID-19 Pandemic

*Presenters Bindu H. Akkanti and Bela Patel*

During the COVID-19 pandemic, the Texas Medical Center's 17 major institutions and hospitals collaborated to generate and analyze data to ensure enough patient beds and track the positivity and death rates. During the height of the pandemic, a daily email was sent reporting the number of cases, deaths, hospitalizations, and, later, vaccinations.

A flow model was developed to match the needs of institutions to the acuity level capability (Figure 1). The system was heavily supported by the strong air ambulance system that existed locally and enabled an escalation of care and rapid response. The pulmonary critical care teams were deployed with rotating schedules. Every week, pandemic meetings were held to gather data and determine the best processes for the week ahead. Importantly, the institutional innovation team used deep learning algorithms with the electronic health record to predict mechanical ventilation use. The information was assembled and presented as a singular dashboard to assist the teams. The dashboards created during the pandemic are still used today, even as the threat has decreased.

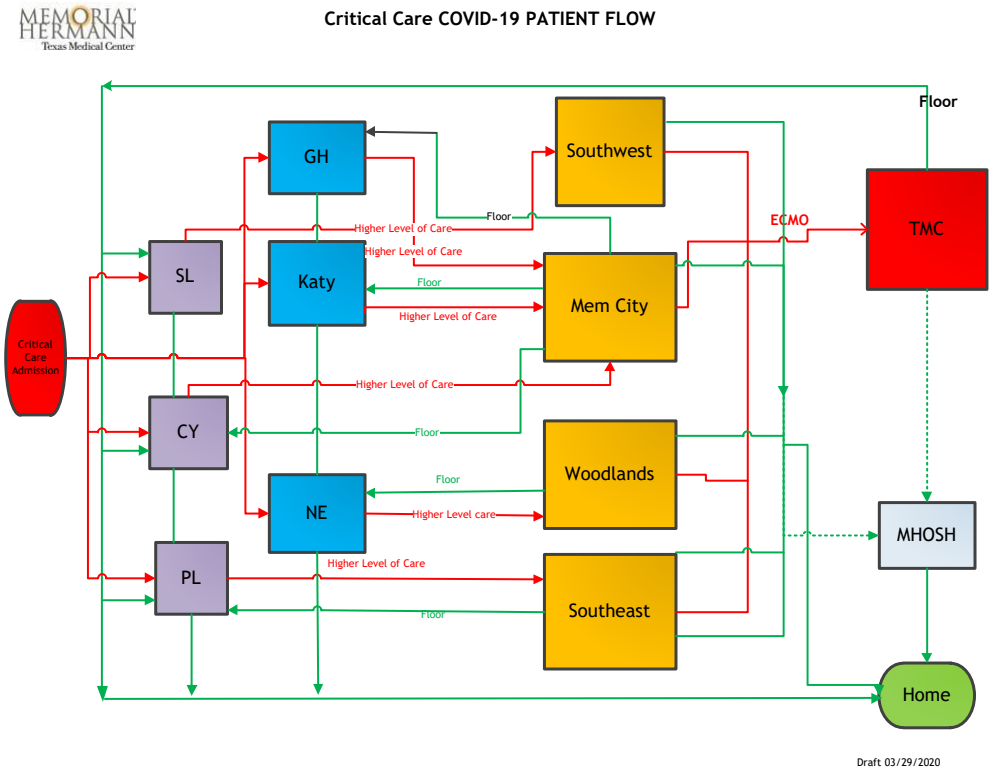



***Figure 1.*** *Strategic plan for the care of critical patients during the pandemic using the resources available in the Greater Houston area.*

The collaboration continues today as the institution manages additional studies on variants and long-term COVID patients. The UTHealth COVID-19 Center of Excellence is dedicated to continuing the work initiated by the pandemic.

## Acute Mechanical Circulatory Support

### ECMO and HemoLung in COVID-19

*Presenter Kha Dinh*

Before the pandemic, our institution initiated a V-V ECMO screening registry to enable further research. COVID-19 dramatically increased the number of ECMO consults, and approximately 31% of those consults resulted in cannulations. We reviewed the outcomes of 277 V-V ECMO consultations (Figure 2). While most were not cannulated, their mortality rate was higher (75% versus 59%).

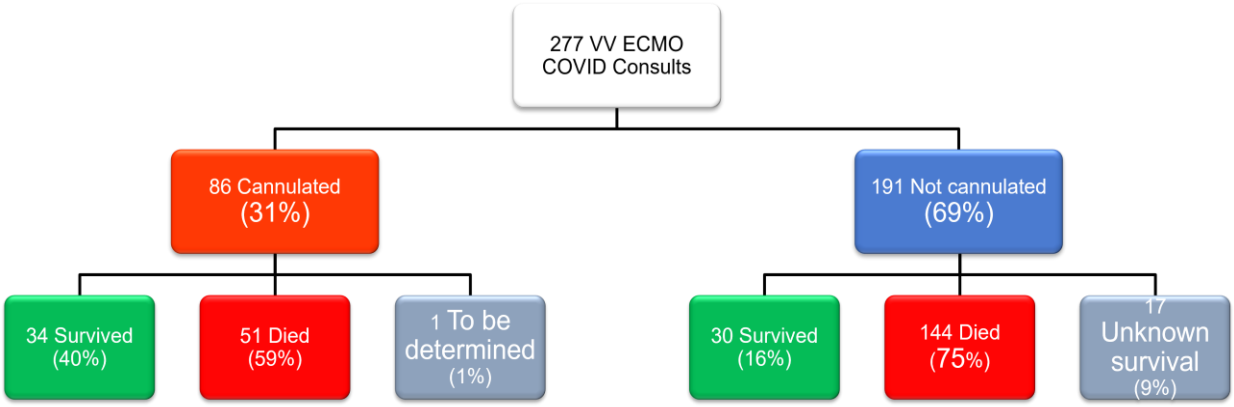



***Figure 2.*** *Outcomes from extracorporeal membrane oxygenation consultations performed at a single center during the pandemic.*

Of note, our patient population's Respiratory ECMO Survival Prediction (RESP) Score did not correlate well with COVID-19 patients. Patients who were not cannulated with a RESP Score ≥6 had a 50/50 chance of survival. We did not cannulate many patients with a score <6 as they have a poor overall prognosis and are difficult to cannulate. More research is needed to provide evidence-based guidance on when we should cannulate.

Maharai and colleagues documented the association between RV dysfunction and mortality in patients with COVID-19 who receive V-V ECMO support.[23] The use of Hemolung's Respiratory Assist System (ALung Technologies, Inc.) for extracorporeal $CO_2$ reduction has shown an initial promise in patients with COVID-19.[24-27]

### ECMELLA 2.0

*Presenter Angelo Nascimbene*

To investigate the impact of Impella (Abiomed) and ECMO use, we have initiated an observational trial at our institution, TWEET. The trial was designed on a retrospective analysis of patients with veno-arterial (V-A) ECMO.

We identified 55 different patient-device combinations that can be generalized into four groups. Detailed analysis was completed and centered on patients who did and did not receive extracorporeal cardiopulmonary resuscitation (eCPR). Initial findings show that patients with eCPR had worse outcomes than those in other published studies. For patients without eCPR, a significant survival difference was found in Impella 5.5 recipients compared to those with an intra-aortic balloon pump (IABP) or no device.

### Surgical Techniques of Ecmella 2.0 and 2.1

*Presenter Evgenij V. Potapov*

Our institution has developed a technique to use single arterial access to insert both the Impella 5.5 and arterial cannula of the extracorporeal life support (ECLS).[28] The Impella must be implanted first and fixated. Then the arterial cannula can be placed. In total, the use of this combined technology allows a total flow of 11-12 L/min (5-5.5 L/min [Impella] and 5-6 L/min [ECLS]).

We improved this technique to allow for mobilization and refer to it as Ecmella 2.1. The improvement means the venous cannula will be implanted into the right jugular vein. The Ecmella 2+ has been done over 60 times at our institution. Our experience indicates an effective modality to improve care for these severely ill patients.

## New Left Ventricular Assist Devices on the Horizon

### CH-VAD

*Presenter Frank Lin*

The CH-VAD®, also known as the Vinovi™ VAD, is an ultra-compact centrifugal pump with total magnetic suspension (Figure 3). It requires pericardial placement, enabling a maximum normal flow of 10 L/min. It has a wearable configuration with one or two external batteries. It recently obtained NMPA PMA approval and started commercialization in China in 2021. The Vinovi VAD has only four leads, and the percutaneous cable is only 3.3 mm; thus, it has the thinnest flexible cable with redundancy to reduce infection and improve reliability. It is also the smallest pump of its kind with a diameter of 47 mm and thickness of 25 mm, which can potentially

support a broader heart failure patient population with a minimally invasive surgical approach.

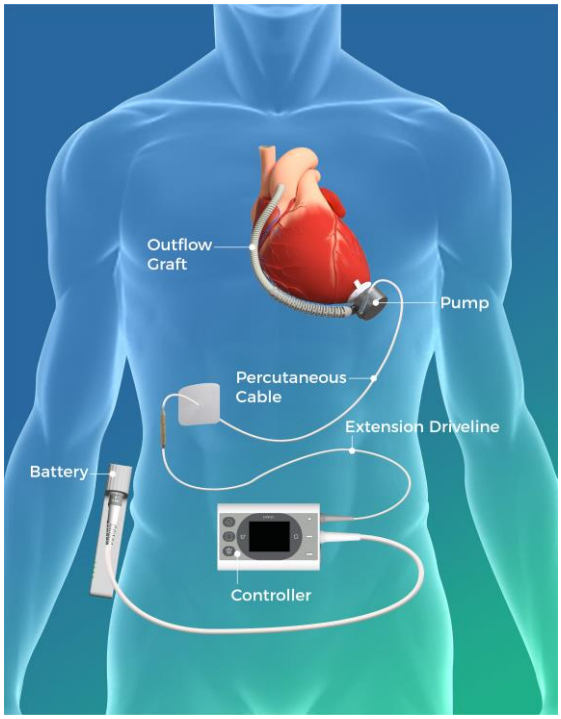



***Figure 3.*** *Vinovi™ Ventricular Assist Device*

**FineHeart**

*Presenter Francis Pagani*

The implantable cardiac output management system uses an axial flow rotary pump which results in low shear stress. The device can produce upward axial driving force (hydraulic force) toward the aortic valve and downward axial driving force (magnets-induced force). Thus, it can maintain the main and reverse flow for washing. It is a synchronized pump that provides pulsatile and continuous flow modes of operation synchronized to native heart rhythms. It has been tested and fits the FDA safety standards for in-vitro hemolysis tests (ASTM-1841).

**TORVAD**

*Presenter Richard Smalling*

After a humble beginning in 2003, the TORVAD family of left ventricular assist devices (LVADs) has evolved to include the TORVAD 30 (full support) and the TORVAD 15 (partial support) devices. While current LVADs utilize continuous flow technology and

are larger, the TORVAD is smaller and uses gentle pumping that minimizes adverse events, such as gastrointestinal (GI) bleeding, stroke, and infections. It provides synchronous, positive displacement, and pulsatile support. In fact, it is very gentle and can pump like a live fish. The technology is "smart" in that a programmed pump can automatically adjust when the heart rate and pressure go down. The vital signs can be transmitted electronically and in real-time. The TORVAD 30 uses wireless power (up to six hours). Both bench and animal data have been collected to support the device's efficacy and safety. The TORVAD 15 device is ideal for the pediatric population. Preclinical testing in the ovine model is ongoing, and further testing and optimization are underway.

## Pharmacology Therapies in Heart Failure Management

### Novel Therapeutic Options for ATTR Amyloidosis

*Presenter Sabina Frljak*

Amyloid cardiomyopathy is becoming prevalent, with the number of cases increasing regularly. Most amyloid cardiomyopathies are categorized into AL amyloidosis (immunoglobulin light-chain aggregation) or Transthyretin (TTR) amyloidosis (ATTR).[29-31] ATTR results from a tetramer precursor, TTR, in the liver, which dissociates to monomers and results in the misfolding of insoluble fragments forming amyloid fibrils. ATTR has two types: hereditary (ATTRv) and wild type (ATTRwt). ATTRv is caused due to mutations in the TTR gene; these patients have polyneuropathy, cardiomyopathy, or mixed phenotype. Eighty percent of older male patients have ATTRwt.[29] Although this is not a rare disease, in most cases, patients go unrecognized, leading to 12% of the heart failure population. Among patients with reduced ejection fraction (EF), 10% are ATTR patients.[32] ATTR patients experience complications like thromboembolic events, conduction disorders, aortic stenosis, heart failure, atrial fibrillation, and ventricular arrhythmias.[33] Various treatment approaches include:

1. suppression of TTR synthesis in the liver,
2. TTR stabilization, and
3. TTR disruption or elimination.

To date, Tafamidis is the only drug approved to treat TTRwt and TTRv cardiomyopathy and has been confirmed in a randomized, placebo-controlled trial. Tafamidis binds to the tiroxine binding site, stabilizes the tetramere, and prevents amyloid formation.[34] Using tafamidis treatment, the ATTR-ACT clinical trial demonstrated that the all-cause mortality was reduced by 30% in the treatment group.[35] A decline in exercise capacity was slowed, and quality of life improved at 30 months.[35] A long-term extension study showed that higher doses of Tafamidis resulted in positive effects on all-cause mortality, hospitalization rate, quality of life, and safety profile.[36] The 5-year data from

the LTE and ATTR-ACT studies revealed a 41% reduction in all-cause mortality with early treatment using Tafamidis.[37] Of note, patisiran is another drug to consider for patients with polyneuropathy. [33]

## Sarcomere Protein Modulation

*Presenters Mattia Zampieri and Iacopo Olivotto*

Sarcomere protein modulator (SPM) is a newly developed drug for hypertrophic cardiomyopathy (HCM) sarcomeres. HCM can lead to sudden deaths in patients with heart failure. In HCM, there is a greater number of active myosin heads that leads to many cross bridges, resulting in excess contractility and impaired relaxation. SPM reduces the active state of myosin filaments, reducing cross bridges and relaxation. The EXPLORER-HCM study revealed that mavacamten treatment reduced the resting LV obstruction and improved quality of life. There was also a slight reduction in LVEF.[38] Myosin inhibitors play a role where standard drugs like beta blockers and disopyramide are less effective with LV obstruction. Various phenotypic changes of HCM include reduced LV outflow tract size, reduced subaortic curtain excursion, increased mitral leaflet size, hyperdynamic LV, reduced LV cavity size, effect on flow direction, and abnormal papillary muscles chordal slack.

## SGLT2 Inhibitors: Novel Evidence

*Presenter Vojtech Melenovsky*

DAPA-HF, DELIVER, EMPEROR-reduced, EMPEROR-preserved, and SOLOIST-WHF are important clinical trials supporting the use of sodium glucose cotransporter 2 (SGLT2i) in patients with heart failure, with the primary outcomes being heart failure hospitalization and CV death.

The DELIVER trial enrolled 6263 patients with EFs >40% regardless of previous EF. Dapagliflozin (10 mg/d) or placebo was administered, and patients were followed for more than 2 years. The results were positive, with reduced heart failure hospitalizations. This study re-confirmed the positive results of the EMPEROR-preserved study. Patients with previously low EFs saw improvement, and those with EFs >60% also benefited from the drug in the DELIVER trial, which was not observed in earlier studies. Additionally, multiple secondary outcomes were reported, including improved quality of life, demonstrated safety data in the elderly and sicker patients with heart failure, and no significant incidences of ketoacidosis, hypoglycemia, or Fournier's gangrene. Of note, the drug was well tolerated.[39]

The meta-analysis of these 5 SGLT2i trials demonstrated a 28% reduction in heart failure hospitalizations during the 27-month follow-up, a 13% reduction in CV death,

and an 8% reduction in all-cause deaths. These outcomes were not affected by EF, age, gender, diabetes mellitus (DM) status, recent heart failure hospitalization history, estimated glomerular filtration rate, body mass index strata, aldosterone receptor antagonists (MRA) use, or angiotensin receptor neprilysin inhibitor (ARNI) use.[40]

The meta-analysis of the DELIVER and DAPA-HF studies, which have similar end-points and methodologies, revealed that SGLT2i provides benefits even in patients with supranormal EF in contrast to ARNI, angiotensin II receptor blockers, and MRA; SGLT2i can be prescribed even without EF data.[41]

Does SGLT2i work for advanced heart failure patients? There was little improvement with respect to New York Heart Association class when SGLT2i was used, but this was not confirmed in other studies.[40] Patients with longer duration of heart failure benefited the most from SGLT2i; however, this was not the case in frail patients.[42] In the DAPA-HF trial, more frail patients have a higher benefit from SGLT2i treatment.[43]

The safety of these drugs in patients after heart transplantation was not tested. In renal transplant patients, there was improved glucose control with no adverse safety issues.[44,45] Positive observational data was reported for patients with LVADs that took SGLT2i; this data was presented at the 2021 Heart Failure Society of America and the 2022 International Society for Heart and Lung Transplantation (ISHLT) meetings.

SGLT2i may not be used in chronic heart failure conditions but can be used in managing acute cardiac decompensation. The EMPULSE trial enrolled 530 patients with acute decompensated heart failure and administered 10 mg/day of empagliflozin or placebo beginning on the 1$^{st}$-5$^{th}$ day of admission for 90 days. The clinical benefit rate was higher in the treatment group (53.9%) compared to the placebo group (39.7%).[46]

In the EMPAG-HF trial, the early addition of 25 mg of empagliflozin to the standard diuretic therapy increased urine output without affecting renal function. Thus, SGLT2i has a renoprotective effect after hospitalization in patients with acute decompensated heart failure.[47]

The nephroprotective effect of SGLT2i in the DAPA-CKD trial was shown to be positive, with a 29% reduction of CV mortality and heart failure hospitalization and a 31% reduction in total mortality in patients with some renal impairment.[48] This nephroprotective effect of SGLT2i is independent of the presence of DM, heart failure, or chronic kidney disease etiology as seen in patients with glomerulonephritis due to autoimmune IgA nephropathy.[49]

Patients who should not be treated with SGLT2i include those with end-stage renal failure (estimated glomerular filtration rate <20-30 ml/min), T1DM or T2DM without endogenous insulin secretion, active urinary tract infection, or intractable genital mycotic infections. However, insufficient data exist on specific patient populations,

including those with severe decompensated heart failure, individuals requiring inotropes, patients with LVADs, and children with heart failure.

## Update on Guidelines for Heart Failure Treatments

*Presenter Marco Metra*

The European Society of Cardiology task force comprises 31 authors and 64 reviewers and is endorsed by 7 associations, 5 councils, and 7 working groups. The society suggests the addition of one or more task force members who are involved in the process of formulating the guidelines. The ESC is updating the guidelines for heart failure for the first time in three years. The updated guidelines consist of 7 new concepts, 41 new recommendations, and 15 changes in recommendations. All the recommendations in the guidelines are based on a voting system where at least 75% of the task force members agree. Although complicated, the process results in a conservative approach to updating guidelines.

The following values are important in the diagnostic algorithm for heart failure considered in the guidelines. With the onset of symptoms in heart failure patients, B-type natriuretic peptide (BNP) levels are measured; a heart failure diagnosis is unlikely with normal levels. If the levels are high, echocardiography is needed to characterize the patient. EF is another important factor for heart failure diagnosis and classification. There are three groups based on EF: 1) reduced EF (REF) ≤ 40%, 2) mid-range EF (MREF) 41-49%, and 3) preserved EF (PEF) ≥ 50%.[50]

SGLT2 inhibitors (empagliflozin in the EMPEROR trial and dapagliflozin in the DELIVER trial) are the only drugs currently effective in patients with EFs >40%. According to recent studies, EFs might not be the only factor to consider in treating heart failure. Increased natriuretic peptides, abnormal echocardiograms, consistent heart failure with PEF, left atrial dilatation, and LV hypertrophy also play significant roles. Drugs that act on neurohormonal systems, including mineralocorticoid antagonists, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I), and ARNI, are effective in patients with REF but not in individuals with PEF.

In the AFFIRM–AHF trial, administration of intravenous ferric carboxymaltose in heart failure patients with an EF <50% reduced re-hospitalizations. Vericiguat (the VICTORIA HF trial) and omecamtiv mecarbil (the GALACTIC HF trial) demonstrated a statistically significant reduction in the primary outcome of mortality and heart failure hospitalizations.[51]

From clinical trial data, pharmacological treatments indicated for patients with heart failure with reduced EF ≤40 include ACE-I, beta-blockers, and aldosterone receptor antagonists (MRA). These medications are mandatory treatment recommendations, whereas dapagliflozin and empagliflozin are recently added drugs. Of note,

sacubitril/valsartan were recommended to replace ACE-I in these patients, and lower doses of ARNI were recommended to be first-line line therapy in heart failure patients with reduced EF.[50]

For patients with volume overload, diuretics are recommended. In patients with advanced heart failure who cannot tolerate ACE-I, ARNI, MRA, or beta-blockers due to hypertension, kidney dysfunction, hyperkalemia, or bradycardia, heart transplantation or MCS as a bridge to transplantation or destination therapy are recommended.[50]

## Vericiguat Therapy

*Presenter Gregor Poglajen*

Heart failure is present in 1-2% of the general population and in >10% of the population over 65-70 years of age with a poor prognosis (50% mortality in 5 years).[52,53] Despite various state-of-the-art medical and device management, patients with chronic heart failure remain at increased risk for CV mortality.[54-58] Patients in New York Heart Association classes III and IV need additional therapeutic options.[59]

Vericiguat works by enhancing the sensitivity of soluble guanylyl cyclase (sGC) to nitric oxide, stimulating sGC and, in turn, cytoplasmic cGMP. This mitigates the effect of cGMP deficiency, which causes myocardial dysfunction and vascular dysfunction.[60]

In the VICTORIA trial, the vericiguat treatment group benefited with reduced CV mortality, total hospitalizations for heart failure, and all-cause mortality. However, there were safety concerns regarding hypotension. Vericiguat therapy was associated with a mild decrease in systolic blood pressure (SBP) at the beginning of the treatment, but the drug's efficacy persisted regardless of baseline SBP. Still, this drug was well tolerated by the high-risk patient population. Anemia was another concern with this treatment, but it did not affect the clinical results or benefits.[60]

With regard to clinical outcomes and NT-proBNP, a reduction in the primary endpoint and its components were observed; patients with NT-proBNP levels up to 8000 pg/mL were likely to benefit from this treatment. In addition, clinical benefits of vericiguat are inversely related to troponin serum levels.[61]

Patients with lower heart failure biomarkers are more likely to display a beneficial response to vericiguat. Conversely, increased hs-cTnT and NT-proBNP predict poor response to vericiguat with poor clinical outcomes. With respect to current optimal medical therapy, vericiguat treatment helps in decreasing the mortality rate with improved clinical outcomes in heart failure patients. Based on data from the VICTORIA, vericiguat remains an add-on therapy.[62,63] In the Medical Center of Ljubljana, we have a patient population similar to that of the VICTORIA trial, who were treated with SGLT2i and vericiguat. The majority of them tolerated the drug well.

Among the total of 28 patients, 1 died, 3 discontinued the treatment due to heart transplantation, and 1 reported symptomatic hypotension.

## Heart Failure Pathology and Novel Treatments

### Update on Treatments of Critical Bleeding in Heart Surgery

*Presenter Arthur Bracey*

Hemostasis is a healing process where platelets start aggregating when an injury or defect in the vascular system occurs. This is due to the large ligands and receptors on the platelets that get tethered to the site, which also activates the platelets to bind to each other resulting in platelet accumulation.[64] Prothrombin time test/international normalized ratio and partial thromboplastin time give only some information about the complex process. Hence, we need a test that provides more information on this process to prescribe treatment for bleeding during surgery.

Instead of being distributed all over the blood, platelets are on the periphery to take care of the injuries to the vessels. There is widespread utilization of blood ranging from 10% to 70% during the intra- and postoperative process (Society of Thoracic Surgeons [STS] Registry). Per the 2021 STS guidelines, goal-directed transfusion algorithms, which incorporate point of care (POC) testing (ie, viscoelastic devices), are recommended to reduce periprocedural bleeding and transfusion in cardiac surgical patients.[65] One of a few advantages of POC testing over those performed in the main lab is that it has a quicker turnaround time by using whole blood as the sample. Although using POC does not reduce morbidity or mortality, it does significantly reduce the use of blood components like red blood cells (RBC), white blood cells, and platelets.[66]

Sonic and ultrasound waves are evolving techniques to identify blood clots. Most of the information about blood is obtained using these techniques; however, studies on P2Y12 and thromboxane pathway inhibition are obtained via thromboelastography (TEG) analysis. At our center, we developed an algorithm for cardiac surgery transfusion, which significantly reduced the use of platelets, plasma, and other blood components and maintained good outcomes. We compared various blood components usage in complex CV surgery and found no significant change in the usage of blood components, except for RBC. Thus, POC testing reduces blood transfusion in CV surgery. However, whole blood transfusion did not impact complex CV surgery in our single-center study.

## Update on Myocarditis and Pericarditis Treatment

*Presenter Massimo Imazio*

The inflammasome is one of the important therapeutic targets for myopericardial diseases. It is a complex of cytosolic proteins activated by various agents like bacteria, viruses, trauma, surgery, irritants, etc. when they encounter pericardial cells during the inflammatory process. This process activates IL-1α, which triggers inflammasomes and IL-1β through monocytes and macrophages. Colchicine is a non-specific inflammasome inhibitor as it prevents the assembly of cytosolic proteins from forming the complex, whereas Anakinra inhibits 1L-1β and is a recombinant IL-1 receptor antagonist. Canakinumab (human monoclonal antibody for IL-1β) might not be effective for pericarditis as it cannot inhibit IL-α. Rilonacept (IL-α and IL-1β trap) is used to treat pericarditis.[67-69] Animal studies have demonstrated that colchicine prevents disease progression in viral myocarditis by modulating the NLRP3 inflammasome.[70] This study described improved EF and reduced troponin levels without increasing the viral load. Some side effects associated with the drugs used for pericarditis treatment include >50% of transient local skin reactions, 4-5% increase of transaminases, 2-3% increased risk of respiratory and skin infections, and <1% reduction of white blood cells.

## Stem Cells

*Presenter Bojan Vrtovec*

Although the pathophysiology of heart failure with preserved ejection fraction (HFpEF) is heterogeneous, one of the important phases in this disease process is the endothelial cell inflammation and microvascular inflammation leading to vascular distraction.[71] This process is confirmed by studies in patients with HFpEF who had lower coronary microvascular density with severe fibrosis.[72] We hypothesize that HFpEF is associated with microvascular dysfunction. Studies have shown that diastolic dysfunction appears to correlate with areas of myocardial scar and hibernation. Transendocardial CD34+ cell transplantation may improve diastolic parameters.

This cell therapy reduced the E/e' ration after six months of treatment in a cohort of patients with non-ischemic dilated cardiomyopathy. It maintained the low ratio for up to one year.[73] Hence, we are evaluating the effects of transendocardial CD34+ cell transplantation in patients with HFpEF. Electroanatomical mapping revealed that diastolic dysfunction in HFpEF is more local than systemic. There were significant changes in the LV filling pressures and NT-proBNP levels, which went down in phase 2 after cell therapy. There was also improvement in the local systolic strain at cell injection sites. The data are promising, considering it is the first clinical study to evaluate the effects of cell therapy in patients with HFpEF.[74]

Due to under-perfused bone marrow, the number of stem cells in heart failure patients is smaller than that in healthy individuals.[75] Even if there are enough stem cells, patients with heart failure conditions suffer from lower homing factors. Stem cells in patients with heart failure do not home to the myocardium. Patients with non-ischemic dilated cardiomyopathy have a lower myocardial expression of stem cell homing factors when compared to ischemic cardiomyopathy patients.[76]

After LVAD implantation, there is an increase in the number of circulating CD34+ cells, in parallel to a reduction in BNP levels.[77] Injection of bone marrow fractions into the heart during LVAD implantation failed to increase tissue vascularity or decrease fibrosis.[78] Hence, we hypothesize that stem cell therapy after recovery from LVAD implantation is better than concurrent therapy at the time of LVAD placement. We conducted the therapy in one patient through intracoronary delivery. The results were promising, with a very high retention rate of stem cells in the myocardium and increased perfusion even after three months of follow-up. Although further research is required to confirm the results, stem cell therapy after LVAD placement appears more effective than the concurrent approach.

**Myocarditis in an Advanced Heart Failure Population-Spectrum of Cardiac and Vascular Involvement in COVID-19**

*Presenter L Maximilian Buja*

The etiology of inflammatory heart disease broadly includes autoimmune, toxic, and infectious factors.[79] Cardiovascular magnetic resonance (CMR) is becoming more popular among the various diagnostic tests for inflammatory heart disease. It provides strong evidence for myocardial inflammation with increasing specificity if at least one T1-based criterion (increased myocardial T1, extracellular volume, or late gadolinium enhancement) and one T2-based criterion (a global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2- weighted CMR images) are met.[80] Endomyocardial biopsy (EMB) also helps to identify and diagnose specific sub-type of myocarditis. A positive biopsy result was observed in 40% of our patient population, which drives more aggressive MCS rather than depending purely on prednisone.

Myocarditis cases are also diagnosed in patients with sarcoidosis. Evaluation of LVAD plugs collected after LVAD placement has provided initial evidence of the correlation, but further research is needed.[81] In the case of COVID-19, the virus initially targets the upper respiratory tract epithelium and endothelium. It also binds to ACE-II receptors with a kinase co-factor. Pathology of this disease includes severe diffuse alveolar damage with microthrombi.[82,83] Microvascular disease could be related to COVID-19 infections, as the virus enters and injures the endothelial cells, releasing Von Willebrand factor (VWF) and P-selectin. Hence, patients with COVID-19 have high

circulating levels of VWF and P-selectin. P-selectin accelerates thrombosis by binding to platelets and mediates vascular inflammation by interacting with leukocytes.[84]

Initial studies on COVID-19 revealed that 40% of patients had higher cardiac troponin levels, indicative of myocardial injury, which might lead to endothelialitis.[85] Per autopsy reports, only 5% of COVID-19 cases had histological evidence of myocarditis. There was increased expression of lymphocytes and inflammation in the myocardium due to increased CD68+ cell expression.[86-88] Evidence of histiocytic myocardial inflammatory disease (HMID) was observed in the hearts of patients with COVID-19, certain non-COVID-related acute heart failure, and other viral infections (ie, Ebola, HIV, and influenza).[89-91] However, HMID might be due to the myocardial involvement by a systemic inflammatory state in the spectrum of multisystem inflammatory syndrome (MIS) +/- macrophage activation syndrome (MAS).

According to studies, the incidence of common viral myocarditis is 1-10 per 100,000 people per year; whereas 100-4000 per 100,000 people with SARS-CoV2 infection suffer myocarditis. After COVID-19 mRNA vaccination, myocarditis incidence is 0.3-5.0 per 100,000 people.[92,93] Clinical observations in the acute myocyte ischemic injury (AMI) group found a significantly higher occurrence of severe primary graft dysfunction. The presence or absence of AMI on the biopsy significantly discriminated between clinical evidence of primary graft dysfunction or not, in which case, biopsy helps to affect the therapy approach. Inflammatory cardiomyopathy is a combination of genetics, infection, and autoimmune factors.[79]

## Inflammatory Heart Disease: Cardio-oncological Entities, including Immune Checkpoint Inhibitor Myocarditis

*Presenter Ana Maria Segura*

Oncological care has shifted to targeted therapy and immunotherapy, which increases the number of cancer survivors and the longevity of these patients. Immunotherapies include immune checkpoint inhibitors (ICI) and chimeric antigen receptor (CAR T-cell) therapies, while targeted therapy consists of tyrosine kinase inhibitors (TKI).

Cancer cells have a defense mechanism that expresses unique tumor antigens recognized by T cells. Simultaneously they inhibit T cell activation by upregulating immune check point molecules, such as programmed death ligand-1 and 2 (PD-L1 and PD-L2) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which counteracts the activity of T-cells.

ICI are monoclonal antibodies that block the immune regulatory proteins leading to T cell destruction of tumors. A side effect of ICI is immune-mediated adverse events like myocarditis.[94] Pathophysiology of CV immune-related adverse events involve activation of T-cells resulting in apoptosis of tumor cells leading to tumor regression,

ultimately improving the survival rate. On the other hand, T- cell activation also results in apoptosis and dysregulation of metabolism in the myocardium and pericardium, which increases the risk of death.[95] A combination of major adverse cardiac events (MACE) with ICI increases the cardiotoxicity rate to 5.8%, while that rate in monotherapy is as low as 3.1%.

There were also incidences of myocarditis, pericarditis, vasculitis, LV dysfunction – arrhythmias, or Takotsubo cardiomyopathy.[96] ICI myocarditis incidence is 1.7% with combination therapy and 0.6% with monotherapy. This disease has a poor prognosis due to pre-existing arrhythmias, low GLS, elevated Tn and lymphocyte infiltration, and a 25-50% mortality rate.[97,98] It also interrupts the cancer treatment

Based on H&E and immunohistochemistry, a grading and scoring system which ranges from 0 to 3+ (negative – cardiomyocyte necrosis) was designed to elucidate the spectrum of ICI myocarditis using endomyocardial biopsy (EMB). This grading system is correlated with a significant increase in troponin levels in grade 2 EMB. The correlation of histological findings with CMR has shown that among 61% of patients on whom CMR was performed, 35% of patients had suggestive or definitive myocarditis.

Some patients could tolerate ICI therapy despite having an inflammatory infiltrate in the myocardium. However, further studies are needed to identify low-risk patients who can be treated safely with ICI. The diagnosis of ICI myocarditis is based on the combination of biomarkers, non-invasive CV imaging (ECG, TTE, or CMR), and EMB. EMB is useful in detecting cancer therapy-related cardiac dysfunction before the onset of irreversible cardiac impairment. It provides clinicians with valuable information, such as changes in chemotherapeutic strategies and timely initiation of cardioprotective strategies.

## Inflammation and Treatments in End-Stage Heart Failure

*Presenter Guillermo Torre-Amione*

Inflammation is associated with a lot of diseases, including CV disease. However, traditional anti-inflammatory therapy is still unable to impact CV disease outcomes.

Tumor necrosis factor (TNF) is highly expressed in chronic HF and cachectic patients.[99] Receptors for TNFα were observed in the myocardium of failing hearts.[100,101] TNF expression was significantly reduced in post-LVAD unloading compared to pre-LVAD unloading.[102] Despite their impressive pre-clinical data, the clinical trials that aimed to inhibit TNF were unsuccessful. IgG was also expressed in failing myocardium, but the proportions were different. The failing myocardium expressed 71% of IgG+, 48% of IgG3+, and 31% of C3c+. In a murine cardiomyopathy model, there was increased B cell and antibody formation.[103]

There is a broad spectrum of immune injury in failing myocardium. The mortality rate was high when ICIs were used in a murine model of heart failure. ICIs also increase heart tissue's BNP, inflammatory cytokines, and CD8+ infiltrates.

On the other hand, cannabidiol (CBD) from cannabis sativa acts as a potent anti-inflammatory source by decreasing angiotensin-mediated hypertrophy and mRNA expression of remodeling markers (ie, BNP, TGFβ, and collagen). It also lowers mitochondrial oxygen-containing reactive species in H9c2 cells. Thus, CBD is a potent anti-hypertrophy, anti-inflammatory and antioxidant mediator. The anti-inflammatory properties of CBD decrease human lymphocyte activation and attenuate adverse remodeling in an ANG II injury model. Currently, CBD is used in a trial enrolling patients with myocarditis to prevent complications of COVID-19.

## Gene Therapy for Treatment of Congestive Heart Failure

*Presenter Thomas J. Povsic*

Most gene therapy targets in preclinical models are genes that are largely dysregulated in heart failure (ie, adenylate cyclase 6, βARK, SERC2A, cardiac I 1-c, urocortin, etc.). Some of these preclinical studies have progressed to clinical studies. We completed a phase 1 study on XC001 (Encoberminogene Rezmadenovec), which expresses three isoforms of VEGF. A phase 2 trial is now enrolling patients with severe angina. The drug, XC001, is administered intramyocardially to target cardiac gene expression. The optimal usage of XC001 maximizes the vector uptake and expression in the target tissue (heart) and minimizes the uptake and effects in other organs (liver, lung, and spleen). The drug is administered surgically using Transthoracic EpiCArdial Procedure (TECAP).

Hurler’s disease is caused by the loss of alpha-1-iduronidase, leading to diffused valve fibrosis, hypertrophy, and a buildup in the heart muscle. A bone marrow transplant can treat this disease, but it is not always effective.[104] Children with Hurler’s disease were treated with a cord blood transplant, and no significant cardiac dysfunction was noted.[105] In a new study, genetically modified hematopoietic stem and progenitor cells were injected into children with Hurler’s disease.[106] Unlike traditional gene therapy, which has limited cardiac applications, novel vectors or technologies have immense potential in genetic analyses and treatment.

## Recovery, Remission, and Rehabilitation

### Medical Therapy to Promote Recovery after Left Ventricle Assist Device Implantation

*Presenter Emma Birks*

Left ventricular unloading with an LVAD is sufficient for myocardial recovery; however, only a few LVADs are explanted. The usual course after LVAD implantation is bridge to transplant or bridge to recovery, while there are usually no assessments of the underlying myocardial function. Also, often there is no attempt to optimize the pump speed to maximize unloading, and there are no attempts to use drug therapy to promote myocardial recovery. Using LVAD support to reverse chronic heart failure requires an aggressive approach, regular, accurate testing, increased unloading, drugs to shrink the heart, techniques to maximize recovery, and explantation with minimal cardiac trauma.

Recovery studies with no heart-failure medications have reported a low recovery rate, in the range of 4% to 8%. Meanwhile, studies with some medications present a higher recovery rate in the 11% to 24% range. Studies with aggressive medical therapy have successful recovery rates of 60% to 73%.[107,108]

The use of beta blockers during LVAD support is not common, but studies have shown that this therapy is well tolerated and can be useful in promoting myocardial recovery.[109,110] Neurohormonal blockade in LVAD patients, especially those receiving triple therapy, has the best survival rate at four years after implantation.[111] LVAD support can induce myocardial recovery and increases the chance of successful recovery with aggressive reverse remodeling therapy. The ISHLT guidelines will be updated to include recommendations for medical therapy during LVAD support.

### Impella 5.5 and Recovery

*Presenter Daniel Zimpfer*

The Impella 5.5 device provides the most physiologic means for LV unloading compared to ECMO and other MCS systems. The surgically implanted Impella 5.5 is the most recent in the family of Impella devices and offers the SmartAssist® technology. This device is FDA-approved for use for up to 14 days, and CE Mark approved for up to 30 days of support. Compared to Impella 5.0, the 5.5 has several design features that make implantation and management easier and provide a slightly higher flow rate. The SmartAssist technology uses sensors for easy repositioning without imaging, helps resolve suction alarms, identifies right heart failure, aids weaning, and uses cloud-based remote monitoring for collaborative patient

management. The 5.5 devices may be implanted through the right or left axillary artery or the anterior aortic root.

In the first 55 patients with cardiogenic shock supported by this device, 64% recovered and were weaned from support, and 20% bridged to other means of support, with an overall survival rate of 84%.[112] Survival and recovery vary by the indication for support, with cardiomyopathy cardiogenic shock having the worst outcomes (36% survival) and post-cardiotomy cardiogenic shock with the best outcomes (94% survival).[113]

## Recovery Post Myocarditis: What Expectations?

*Presenter Enrico Ammirati*

In a contemporary cohort of patients with acute myocarditis, most deaths or transplantations occur during the initial hospitalization, with very few events in the subsequent five years.[114] The clinical presentation has a high prognostic value. A complicated presentation with an EF <50%, sustained ventricular arrhythmias, and cardiogenic shock projects a mortality rate of 10.4% at 30 days and 14.7% at 5 years. In contrast, the uncomplicated presentation has a 0% mortality at 5 years. The prognosis and outcome of COVID-19–associated acute myocarditis is similar to that of the general myocarditis population.[115]

In the population of patients with COVID-19, the presence of pneumonia projected the worst outcome. Patients with histologically proven acute fulminant myocarditis have a much worse prognosis than those with non-fulminant myocarditis at 7 years after diagnosis (48% vs. 10.4%).[116] The predictors of poor outcomes in patients with fulminant myocarditis are the presence of giant cells on histology, prolonged QRS duration, and the need for temporary MCS. Septal fibrosis seen on MRI and the presence of DSP gene variants can help identify a subset of patients at increased risk of poor outcomes, despite having a preserved EF. Most of the changes in EF occur early after the onset of myocarditis, which indicates that this is the time to focus on therapy.

## Recovery after Temporary Device: Ecpella

*Presenter Sana Shoukat*

A 40-year-old male with DM, coronary artery disease, hypertension, and prior percutaneous coronary intervention (PCI) presented with anterior STEMI. Left heart catheterization revealed severe multivessel disease and a culprit left anterior descending coronary artery lesion. The patient underwent PCI, an IABP was placed, and the patient's condition worsened, requiring vasopressors and oxygen. On day 1, the patient was tachycardic, had cool extremities, elevated creatinine and glucose,

LVEF was 30% to 35%, and global hypokinesis was present. V-A ECMO and Impella 5.5 support were instituted. The patient's condition improved over the ensuing five days, V-A ECMO was weaned, he was extubated, and Impella support was continued as a bridge to decision. On day 11, the Impella device thrombosed, and because of cardiogenic shock, V-A ECMO and IABP support was restarted. On day 15, the Impella device was reinserted, V-A ECMO was removed, and all inotropes were weaned. The patient could not be weaned from Impella support, and the HeartMate 3 (HM3) was implanted on day 40 with Impella removal. The patient was discharged home and is rehabilitating.

This case raises the following questions *(audience responses)*: 1) Should we prioritize Impella 5.5 placement in AMI patients with shock? (*Majority, yes)*. 2) What is the role of IABP in the contemporary era of AMI-related shock? (*Majority, no)*. 3) Should everyone with V-A ECMO be vented or fully unloaded? (*Depends on the patient).* 4) What is the real-world experience with Impella thrombosis? (*3% to 5%).* 5). Will MCS selection and weaning remain an art? *(Yes)*

## Early Cardiac Rehabilitation after LVAD Implantation

*Presenter Christiane Marko*

Cardiac rehabilitation has been defined as the sum of interventions required to ensure the best possible physical, psychological, and social condition so that patients with subacute or chronic disease may, by their own efforts, preserve or resume life as normal as possible in the community. The phases of rehabilitation (WHO) are: 1) early in-hospital mobilization, 2) the reconditioning phase, and 3) the maintenance phase. Before rehabilitation for LVAD patients, they must be clinically stable, have no signs of infection, receive heart failure medications, and have optimized blood pressure. The components of the rehabilitation program are medical training, education, psychological counseling, and functional testing. Specific challenges for the LVAD population during rehabilitation need to be accounted for (ie, blood pressure measurement, driveline). Successful rehabilitation after six months has been demonstrated by a mean peak oxygen uptake change from 14.1 ml/kg/min to 47 ml/kg/min, which has an important prognostic value.[117] There are few complications related to rehabilitation, and this program is recommended by expert consensus.[118]

# Mechanical Circulatory Support Management

## Is Ejection Fraction Overrated?

*Presenter Jerry Estep*

EF is overrated, as it is related to durable LVAD management. The classification of EF (HFpEF, mildly reduced EF, HFrEF) is currently being challenged. The variability in LVEF in a high-quality laboratory is 5% to 7%. LVAD support leads to LV unloading characterized by a leftward shift of the pressure-volume loop.[119] The ASE Guidelines and standards on echocardiography metrics will be updated in the first quarter of 2023. In a risk score for survival following LVAD implantation, LVEF was not included in the echocardiography indices, but LV size was included. In multiple studies, the LVEF remained severely depressed one year after LVAD implantation.[120] In an analysis of the INTERMACS registry, only 8.6% of patients had an LVEF >40%, and 90% had no improvement.[121] The LVEF data is important to screen and help define myocardial recovery.[107] There is no known association between LVEF and RV failure, heart failure, or GI bleeding. The following concerns are that LVEF: does not provide information on the underlying pathology, commonly does not change after LVAD implant, may not reflect optimal hemodynamics, is not associated with adverse events, and is the last parameter to consider on the echocardiography report.

## Should We Oversize the Hearts for LVAD-supported Patients?

*Presenter Maya Guglin*

Current ISHLT guidelines recommend using a donor body weight of no more than 30% below the recipients. Early studies have shown that there is an increased mortality in female-to-male transplants. Many centers now use a predicted heart mass ratio of >0.86. There are no specific recommendations for size matching for heart transplant recipients following LVAD support. Historically, many transplant programs oversize donor hearts for recipients with LVADs and avoid female-to-male transplants. In a study from the Scientific Registry of Transplant Recipients (SRTR), five metrics for size matching were used to create three groups: undersized, matched, and oversized. The undersized group had a significantly worse survival ($p$ = 0.0024), and no difference existed between the matched and oversized groups. For heart transplant recipients on LVAD support, undersizing of donor hearts based on a predicted heart mass of 0.82 is associated with higher 1-year mortality. When stratification of donor size is based on other metrics, there is no impact on survival. There is no evidence to support the practice of oversizing donor hearts, and no effect of the donor/recipient sex mismatch on outcomes has been confirmed.

## Preventing Right Heart Failure Exacerbation After LVAD

*Presenter J. Eduardo Rame*

Clinicians prevent exacerbations of right heart failure by monitoring closely, targeting organ-specific reserve, and fully reversing organ dysfunction. The patients being treated with implantation of an LVAD have LV failure and the beginning of RV failure. The LV serves as an anchor to the RV, and the RV function is dependent on the LV function. There is a right-left ventricular interaction post-LV decompression. At three months after LVAD implantation, patients with mild-to-moderate right heart failure have significantly worse mortality and higher rates of rehospitalization, stroke, and GI bleeding than patients with no heart failure.[122] The INTERMACS definition for right heart failure was revised in 2014, which allowed for rehospitalization and clinic signs of failure. At 3, 6, and 12 months after LVAD implant, about 10% of patients have mild-to-moderate right heart failure. Patients without right heart failure have a 3.2% 1-year mortality rate. Preventing right heart failure exacerbation involves drug therapy to reverse myocardial dysfunction and failure. The understanding of late right heart failure is evolving, highlighting that the mortality of mild right heart failure is significant, and all adverse events are increased with right heart failure.

## How to Deal with Atrial Arrhythmias in LVAD Patients

*Presenter Greg Couper*

There are several outstanding questions regarding atrial arrhythmias in patients supported by an LVAD. There is a 21% to 50% incidence of atrial fibrillation (AF) in the heart failure population, which worsens survival, stroke, and hospitalization. The SOLVD trial and the Framingham Heart study have shown that AF increases the risk of stroke, hospitalization, and all-cause mortality. Published studies addressing atrial arrhythmia in the LVAD population present a variable prevalence of 30% to 70%. The disparity is wide in the reported outcomes, but the burden of care is universally high.

Although paroxysmal AF is not associated with worse outcomes in patients with LVADs, persistent AF may be associated with increased mortality and hospitalization.[123] Permanent AF or atrial tachycardia are predictors of higher 1-year mortality. However, numerous studies demonstrate that atrial arrhythmias have little or no effect on survival in the LVAD population. Unloading with the LVAD does help resolve paroxysmal atrial arrhythmias, and there are numerous treatment options for atrial arrhythmias, including amiodarone, Maze procedure, and catheter ablation. Atrial arrhythmias are clearly an added burden, but there is inconclusive proof of AF-related increased mortality. Management strategies have a therapeutic bias, and controlled trials are warranted before supplemental surgical, percutaneous ablation, or additive medical therapies can be universally applied.

### Fixing of the Tricuspid Valve During LVAD Implantation: Some Conceptual Thoughts

*Presenter Georg Weiselthaler*

The pre-implant hemodynamics in end-stage heart failure patients includes low aortic pressure, elevated right and left atrial pressure, low venous oxygen saturation, high wedge pressure, and a bulging LV with mitral regurgitation. Only a few surgeons address the mitral valve during LVAD implantation. The tricuspid valve is addressed when the annulus is > 4 cm. The extent of tricuspid valve repair is in question.

There are several advantages and disadvantages to the repair of tricuspid regurgitation at LVAD implantation. In most cases, tricuspid valve leakage decreases after implant, and the right heart can usually provide adequate flow to the left side. What has worked is to 1) address moderate to severe tricuspid regurgitation; 2) not completely correct the insufficiency (leave 1+); 3) protect the RV but operate the LVAD at a lower pump rate; 4) an $SvO_2$ > 60% immediately postop is not necessary; 5) restrict the use of vasopressors; 6) use inhaled nitric oxide in patients with pulmonary hypertension unresponsive to medical therapy; and 7) use peripheral V-A ECMO for short-term RV unloading.

## Challenges in Mechanical Circulatory Support

### Mechanism and Prevalence of HM3 Outflow Graft Obstruction

*Presenter Ulrich P. Jorde*

The HeartMate II (HMII) device had bend relief disconnection on the outflow graft in approximately 1% of all implants.[124] In the HM3, the connection between the bend relief and the pump has been changed to a swivel joint that can rotate and create an obstruction of the outflow graft. In an early case, surgical intervention was required to untwist the outflow graft, and symptoms improved, but there were still low-flow alarms.[125] Upon catheterization, the graft was untwisted but required stenting to open the graft, which resulted in normal flows. This problem has been resolved by placing a stabilizing clamp on the swivel joint. Most obstructions result from an accumulation of proteinaceous material between the bend relief and the outflow graft. A potential solution is to create a fenestration in the bend relief.[126] The real-world incidence of outflow graft obstruction for all devices is 1.8%, 6.0%, 12.3%, 15.4%, and 16.6% at 1, 2, 3, 4, and 5 years, respectively.[127] One group has placed carotid filters to catch debris during percutaneous intervention for LVAD outflow graft obstruction.[128]

**Is There a Benefit in Thoracotomy Left Ventricular Assist Device Implant**

*Presenter Mehmet Hakan Akay*

A retrospective review of 93 patients who underwent off-pump LVAD implantation by median sternotomy (MS, N = 69) or sternal sparing (SS, N = 24) was performed. The observed differences were that the anesthesia time, surgery time, and intraoperative blood loss were all greater for the SS group. There were no differences in the number of blood products transfused. The two groups had no differences in postoperative outcomes (30-day mortality, survival to discharge, hospital stay, and readmission rate). The results of this study question the common nomenclature. A search on PubMed produced 140 citations for the term “less invasive LVAD.” The incision length for the MS approach is approximately 20 cm, whereas the total incision length for the thoracotomy, subxiphoid incision, and groin incisions used in the SS approach is 36 cm. It is proposed that “sternal sparing” is preferred over “less invasive.”

**Ambulatory Mechanical Circulatory Assist Systems**

*Presenter Valluvan Jeevanandam*

The next-generation MCS should have less surgical trauma for implantation. The major challenges for MCS are access to the heart, adequate level of support, durability, and human movement. Some methods for ambulatory MCS are transvalvular (Impella), aortic positioning (Procyrion Aortix), and counter pulsation (NuPulseCV iVAS). The iVAS, an intravascular ventricular assist system, is designed for long-term ambulatory use. The device is inserted into the descending aorta through a graft anastomosed to the subclavian artery.

In a feasibility trial, 89 patients were implanted with the device, 30 were discharged home, 29 were supported for > 6 months, and 4 patients were supported for more than 1 year. The FDA has approved a pivotal clinical trial; however, the trial was put on hold during the COVID pandemic, and the system has undergone revision to allow for percutaneous insertion. Experience has shown that myocardial reserve is needed, and the cardiac power efficiency is a hemodynamic variable that indicates which patients may benefit from this type of support.

**Impella 5.5 to Facilitate Cardiac Surgery**

*Presenter Scott Silvestry*

In 2022, it became apparent that patients with cardiogenic shock should not undergo immediate corrective surgery. Patients with a EuroSCORE II risk assessment > 10 have poor outcomes. Surgeons should always plan for cardiogenic shock and be

prepared for a "bridge" system. When planning the bridge, consider access, location, amount of support needed, blood path, and anticoagulation.

The use of Impella 5.5 as a bridge to cardiac surgery and its use following high-risk surgery has resulted in extremely high survival rates in high-risk patients. Using ECMO for postoperative shock does not show a significant survival advantage, but preoperative use produces better survival.[129]

Bridge to next therapy may include TAVR with biventricular failure and the potential for LVAD implant or heart transplant. The Impella 5.5 has disrupted how we support patients and has expanded the envelope for patients with shock and LV dysfunction in a multidimensional fashion for conventional and advanced heart failure cardiac surgery patients.

The use of percutaneous devices preoperatively helps to optimize patients with acute decompensated heart failure being considered for surgery. The devices stabilize shock symptoms, allowing for operative planning and often improving survival.

## What Do We Need to Know About HeartMate 3?

*Presenter Nir Uriel*

The overall survival for patients with the HM3 device is 58.4%, which is significantly higher than that for those patients supported by the HMII, at 43.7%.[130] The incidence of right heart failure, other neurological events, and infection was similar between the two groups. In contrast, bleeding, stroke, pump thrombosis, and arrhythmia were significantly better for the patients with a HM3.

For the entire study population, approximately 44% of patients had clinically significant mitral regurgitation (MR) pre-implant, but after LVAD implant, the MR rate decreased to 7% to 9% out to 24 months. At the 24-month timepoint, there was no difference in the composite endpoint or overall survival for patients with significant MR versus those without significant MR. The incidence of right heart failure is significantly higher in HM3-supported patients who had the MR corrected at the time of implant compared with those who did not have MR correction ($p$ = 0.0004).[131] In patients that had tricuspid regurgitation (TR) corrected at HM3 implant, there was significantly longer implant time ($p$ = 0.0001) and cardiopulmonary bypass time ($p$ = 0.0001).

The outcomes and adverse event rates were similar between patients with corrected vs. uncorrected TR. The prevalence of aortic regurgitation is higher for HMII-supported patients than those supported by the HM3 out to 24 months.[132] Ramped speed change studies demonstrated that the HM3 device unloaded the LV with the same effect as the HMII or HVAD devices. There were no differences in the survival and composite

endpoint when comparing sex; however, female patients have high rates of stroke, GI bleeding, and infection.

## References

1. *Management of Bleeding Patients*. Springer; 2016.
2. (ELSO) ELSO. General Guidelines for all ECLS Cases. Ann Arbor, MI, USA2017.
3. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative Major Adverse Cardiovascular and Cerebrovascular Events Associated With Noncardiac Surgery. *JAMA Cardiol*. Feb 1 2017;2(2):181-187. doi:10.1001/jamacardio.2016.4792
4. Akkanti B, Salas De Armas IA, Sachedina AK, et al. Extracorporeal Membrane Oxygenation Utility in Postpartum Patients. *J Extra Corpor Technol*. Sep 2020;52(3):191-195. doi:10.1182/ject-2000021
5. Salas De Armas IA, Akkanti B, Doshi PB, et al. Traumatic respiratory failure and veno-venous extracorporeal membrane oxygenation support. *Perfusion*. Jul 2022;37(5):477-483. doi:10.1177/02676591211012840
6. Salas de Armas IA, Holifield L, Janowiak LM, et al. The use of veno-arterial extracorporeal membrane oxygenation in the octogenarian population: A single-center experience. *Perfusion*. Jun 29 2022:2676591221111506. doi:10.1177/02676591221111506
7. Banjac I, Petrovic M, Akay MH, et al. Extracorporeal Membrane Oxygenation as a Procedural Rescue Strategy for Transcatheter Aortic Valve Replacement Cardiac Complications. *ASAIO J*. Jan-Feb 2016;62(1):e1-4. doi:10.1097/MAT.0000000000000275
8. Salas de Armas IA, Akkanti BH, Janowiak L, et al. Inter-hospital COVID ECMO air transportation. *Perfusion*. May 2021;36(4):358-364. doi:10.1177/0267659120973843
9. Sage AT, Richard-Greenblatt M, Zhong K, et al. Prediction of donor related lung injury in clinical lung transplantation using a validated ex vivo lung perfusion inflammation score. *J Heart Lung Transplant*. Jul 2021;40(7):687-695. doi:10.1016/j.healun.2021.03.002
10. Kakishita T, Oto T, Hori S, et al. Suppression of inflammatory cytokines during ex vivo lung perfusion with an adsorbent membrane. *Ann Thorac Surg*. Jun 2010;89(6):1773-9. doi:10.1016/j.athoracsur.2010.02.077
11. Iskender I, Sakamoto J, Nakajima D, et al. Human alpha1-antitrypsin improves early post-transplant lung function: Pre-clinical studies in a pig lung transplant model. *J Heart Lung Transplant*. Jul 2016;35(7):913-21. doi:10.1016/j.healun.2016.03.006
12. Nuzzi V, Del Mestre E, Degrassi A, et al. Cardiovascular Damage in COVID-19: What We Know Two Years Later. *Curr Cardiol Rep*. Sep 2022;24(9):1085-1091. doi:10.1007/s11886-022-01730-4
13. Lombardi CM, Carubelli V, Iorio A, et al. Association of Troponin Levels With Mortality in Italian Patients Hospitalized With Coronavirus Disease 2019: Results of a Multicenter Study. *JAMA Cardiol*. Nov 1 2020;5(11):1274-1280. doi:10.1001/jamacardio.2020.3538

14. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. Jul 1 2020;5(7):802-810. doi:10.1001/jamacardio.2020.0950
15. Paris S, Inciardi RM, Lombardi CM, et al. Implications of atrial fibrillation on the clinical course and outcomes of hospitalized COVID-19 patients: results of the Cardio-COVID-Italy multicentre study. *Europace*. Oct 9 2021;23(10):1603-1611. doi:10.1093/europace/euab146
16. Tomasoni D, Inciardi RM, Lombardi CM, et al. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. *Eur J Heart Fail*. Dec 2020;22(12):2238-2247. doi:10.1002/ejhf.2052
17. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. Sep 14 2021;42(35):3427-3520. doi:10.1093/eurheartj/ehab364
18. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med*. Apr 25 2013;368(17):1585-93. doi:10.1056/NEJMoa1210356
19. 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
20. 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
21. 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
22. SEMMELWEIS-CRT. Machine Learning Based Prediction of Mortality in Patients Undergoing Cardiac Resynchronization Therapy. https://arguscognitive.com/crt
23. Maharaj V, Alexy T, Agdamag AC, et al. Right Ventricular Dysfunction is Associated with Increased Mortality in Patients Requiring Venovenous Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019. *ASAIO J*. Jun 1 2022;68(6):772-778. doi:10.1097/MAT.0000000000001666
24. Taxiera JJ, Cambria G, Mackay E. Extracorporeal CO(2) reduction for COVID-19: hypercapnic respiratory failure post extracorporeal membrane oxygenation. *BMJ Case Rep*. Feb 25 2022;15(2)doi:10.1136/bcr-2021-246247
25. Saavedra-Romero R, Paz F, Litell JM, et al. Treatment of Severe Hypercapnic Respiratory Failure Caused by SARS-CoV-2 Lung Injury with ECCO(2)R Using the Hemolung Respiratory Assist System. *Case Rep Crit Care*. 2021;2021:9958343. doi:10.1155/2021/9958343
26. Akkanti B, Jagpal S, Darwish R, et al. Physiologic Improvement in Respiratory Acidosis Using Extracorporeal Co(2) Removal With Hemolung Respiratory Assist System in the Management of Severe Respiratory Failure From Coronavirus Disease 2019. *Crit Care Explor*. Mar 2021;3(3):e0372. doi:10.1097/CCE.0000000000000372

27. McNamee JJ, Gillies MA, Barrett NA, et al. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial. *JAMA*. Sep 21 2021;326(11):1013-1023. doi:10.1001/jama.2021.13374
28. Eulert-Grehn JJ, Starck C, Kempfert J, Falk V, Potapov E. ECMELLA 2.0: Single Arterial Access Technique for a Staged Approach in Cardiogenic Shock. *Ann Thorac Surg*. Feb 2021;111(2):e135-e137. doi:10.1016/j.athoracsur.2020.06.084
29. Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med*. Dec 2017;84(12 Suppl 3):12-26. doi:10.3949/ccjm.84.s3.02
30. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. Jan 2018;28(1):10-21. doi:10.1016/j.tcm.2017.07.004
31. Kholova I, Niessen HW. Amyloid in the cardiovascular system: a review. *J Clin Pathol*. Feb 2005;58(2):125-33. doi:10.1136/jcp.2004.017293
32. Aimo A, Merlo M, Porcari A, et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail*. Dec 2022;24(12):2342-2351. doi:10.1002/ejhf.2532
33. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. Apr 21 2021;42(16):1554-1568. doi:10.1093/eurheartj/ehab072
34. Bulawa CE, Connelly S, Devit M, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. *Proc Natl Acad Sci U S A*. Jun 12 2012;109(24):9629-34. doi:10.1073/pnas.1121005109
35. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med*. Sep 13 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689
36. Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail*. Feb 2021;23(2):277-285. doi:10.1002/ejhf.2027
37. Elliott P, Drachman BM, Gottlieb SS, et al. Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy. *Circ Heart Fail*. Jan 2022;15(1):e008193. doi:10.1161/CIRCHEARTFAILURE.120.008193
38. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. Sep 12 2020;396(10253):759-769. doi:10.1016/S0140-6736(20)31792-X
39. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. Sep 22 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286
40. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled

trials. *Lancet*. Sep 3 2022;400(10354):757-767. doi:10.1016/S0140-6736(22)01429-5

41. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. Sep 2022;28(9):1956-1964. doi:10.1038/s41591-022-01971-4
42. Yeoh SE, Dewan P, Jhund PS, et al. Patient Characteristics, Clinical Outcomes, and Effect of Dapagliflozin in Relation to Duration of Heart Failure: Is It Ever Too Late to Start a New Therapy? *Circ Heart Fail*. Dec 2020;13(12):e007879. doi:10.1161/CIRCHEARTFAILURE.120.007879
43. Butt JH, Dewan P, Merkely B, et al. Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction : A Post Hoc Analysis of the DAPA-HF Trial. *Ann Intern Med*. Jun 2022;175(6):820-830. doi:10.7326/M21-4776
44. Halden TAS, Kvitne KE, Midtvedt K, et al. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. *Diabetes Care*. Jun 2019;42(6):1067-1074. doi:10.2337/dc19-0093
45. Schwaiger E, Burghart L, Signorini L, et al. Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. *Am J Transplant*. Mar 2019;19(3):907-919. doi:10.1111/ajt.15223
46. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. Mar 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1
47. Schulze PC, Bogoviku J, Westphal J, et al. Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). *Circulation*. Jul 26 2022;146(4):289-298. doi:10.1161/CIRCULATIONAHA.122.059038
48. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. Oct 8 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816
49. Wheeler DC, Toto RD, Stefansson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int*. Jul 2021;100(1):215-224. doi:10.1016/j.kint.2021.03.033
50. 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
51. Tomasoni D, Adamo M, Anker MS, von Haehling S, Coats AJS, Metra M. Heart failure in the last year: progress and perspective. *ESC Heart Fail*. Dec 2020;7(6):3505-3530. doi:10.1002/ehf2.13124
52. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart

Failure Association (HFA) of the ESC. *Eur J Heart Fail*. Aug 2012;14(8):803-69. doi:10.1093/eurjhf/hfs105

53. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. Oct 15 2013;62(16):e147-239. doi:10.1016/j.jacc.2013.05.019
54. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. Jan 6 2011;364(1):11-21. doi:10.1056/NEJMoa1009492
55. McMurray JJ, Packer M, Solomon SD. Neprilysin inhibition for heart failure. *N Engl J Med*. Dec 11 2014;371(24):2336-7. doi:10.1056/NEJMc1412654
56. McMurray JJV, Docherty KF, Jhund PS. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. Reply. *N Engl J Med*. Mar 5 2020;382(10):973. doi:10.1056/NEJMc1917241
57. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. Jan 2 1999;353(9146):9-13.
58. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. Aug 1 1991;325(5):293-302. doi:10.1056/NEJM199108013250501
59. Jhund PS, Ponikowski P, Docherty KF, et al. Dapagliflozin and Recurrent Heart Failure Hospitalizations in Heart Failure With Reduced Ejection Fraction: An Analysis of DAPA-HF. *Circulation*. May 18 2021;143(20):1962-1972. doi:10.1161/CIRCULATIONAHA.121.053659
60. Armstrong PW, Roessig L, Patel MJ, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator: The VICTORIA Trial. *JACC Heart Fail*. Feb 2018;6(2):96-104. doi:10.1016/j.jchf.2017.08.013
61. Ezekowitz JA, O'Connor CM, Troughton RW, et al. N-Terminal Pro-B-Type Natriuretic Peptide and Clinical Outcomes: Vericiguat Heart Failure With Reduced Ejection Fraction Study. *JACC Heart Fail*. Nov 2020;8(11):931-939. doi:10.1016/j.jchf.2020.08.008
62. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail*. Feb 2022;10(2):73-84. doi:10.1016/j.jchf.2021.09.004
63. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. May 3 2022;145(18):e876-e894. doi:10.1161/CIR.0000000000001062
64. Fogelson AL, Neeves KB. Fluid Mechanics of Blood Clot Formation. *Annu Rev Fluid Mech*. Jan 1 2015;47:377-403. doi:10.1146/annurev-fluid-010814-014513

65. Tibi P, McClure RS, Huang J, et al. STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management. *Ann Thorac Surg*. Sep 2021;112(3):981-1004. doi:10.1016/j.athoracsur.2021.03.033
66. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. *Br J Anaesth*. Jun 1 2017;118(6):823-833. doi:10.1093/bja/aex100
67. Imazio M, Andreis A, De Ferrari GM, et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: The IRAP (International Registry of Anakinra for Pericarditis) study. *Eur J Prev Cardiol*. Jun 2020;27(9):956-964. doi:10.1177/2047487319879534
68. Brucato A, Imazio M, Gattorno M, et al. Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence: The AIRTRIP Randomized Clinical Trial. *JAMA*. Nov 8 2016;316(18):1906-1912. doi:10.1001/jama.2016.15826
69. Klein AL, Imazio M, Cremer P, et al. Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent Pericarditis. *N Engl J Med*. Jan 7 2021;384(1):31-41. doi:10.1056/NEJMoa2027892
70. Pappritz K, Lin J, El-Shafeey M, et al. Colchicine prevents disease progression in viral myocarditis via modulating the NLRP3 inflammasome in the cardiosplenic axis. *ESC Heart Fail*. Apr 2022;9(2):925-941. doi:10.1002/ehf2.13845
71. D'Amario D, Migliaro S, Borovac JA, et al. Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction. *Front Physiol*. 2019;10:1347. doi:10.3389/fphys.2019.01347
72. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. Feb 10 2015;131(6):550-9. doi:10.1161/CIRCULATIONAHA.114.009625
73. Bervar M, Kozelj M, Poglajen G, et al. Effects of Transendocardial CD34(+) Cell Transplantation on Diastolic Parameters in Patients with Nonischemic Dilated Cardiomyopathy. *Stem Cells Transl Med*. Jun 2017;6(6):1515-1521. doi:10.1002/sctm.16-0331
74. Vrtovec B, Frljak S, Poglajen G, et al. A pilot clinical trial of cell therapy in heart failure with preserved ejection fraction. *Eur J Heart Fail*. Aug 2022;24(8):1441-1449. doi:10.1002/ejhf.2596
75. Valgimigli M, Rigolin GM, Fucili A, et al. CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. *Circulation*. Sep 7 2004;110(10):1209-12. doi:10.1161/01.CIR.0000136813.89036.21
76. Theiss HD, David R, Engelmann MG, et al. Circulation of CD34+ progenitor cell populations in patients with idiopathic dilated and ischaemic cardiomyopathy (DCM and ICM). *Eur Heart J*. May 2007;28(10):1258-64. doi:10.1093/eurheartj/ehm011
77. Manginas A, Tsiavou A, Sfyrakis P, et al. Increased number of circulating progenitor cells after implantation of ventricular assist devices. *J Heart Lung Transplant*. Jul 2009;28(7):710-7. doi:10.1016/j.healun.2009.04.006

78. Stempien-Otero A, Helterline D, Plummer T, et al. Mechanisms of bone marrow-derived cell therapy in ischemic cardiomyopathy with left ventricular assist device bridge to transplant. *J Am Coll Cardiol*. Apr 14 2015;65(14):1424-34. doi:10.1016/j.jacc.2015.01.042
79. Trachtenberg BH, Hare JM. Inflammatory Cardiomyopathic Syndromes. *Circ Res*. Sep 15 2017;121(7):803-818. doi:10.1161/CIRCRESAHA.117.310221
80. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol*. Dec 18 2018;72(24):3158-3176. doi:10.1016/j.jacc.2018.09.072
81. Buja LM, Ottaviani G, Ilic M, et al. Clinicopathological manifestations of myocarditis in a heart failure population. *Cardiovasc Pathol*. Mar-Apr 2020;45:107190. doi:10.1016/j.carpath.2019.107190
82. Buja LM, Wolf DA, Zhao B, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. *Cardiovasc Pathol*. Sep-Oct 2020;48:107233. doi:10.1016/j.carpath.2020.107233
83. Barth RF, Buja LM, Barth AL, Carpenter DE, Parwani AV. A Comparison of the Clinical, Viral, Pathologic, and Immunologic Features of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus 2019 (COVID-19) Diseases. *Arch Pathol Lab Med*. Oct 1 2021;145(10):1194-1211. doi:10.5858/arpa.2020-0820-SA
84. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. *Circulation*. Oct 27 2020;142(17):1609-1611. doi:10.1161/CIRCULATIONAHA.120.050354
85. Sandoval Y, Januzzi JL, Jaffe A. Cardiac Troponin Increases Indicative of Myocardial Injury Common in COVID-19 Patients, Associated With Adverse Outcomes. *Am Coll Cardiol*. July 08 2020; (ACC News Story)
86. Kawakami R, Sakamoto A, Kawai K, et al. Pathological Evidence for SARS-CoV-2 as a Cause of Myocarditis: JACC Review Topic of the Week. *J Am Coll Cardiol*. Jan 26 2021;77(3):314-325. doi:10.1016/j.jacc.2020.11.031
87. Buja LM, Stone JR. A novel coronavirus meets the cardiovascular system: Society for Cardiovascular Pathology Symposium 2021. *Cardiovasc Pathol*. Jul-Aug 2021;53:107336. doi:10.1016/j.carpath.2021.107336
88. Bearse M, Hung YP, Krauson AJ, et al. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. *Mod Pathol*. Jul 2021;34(7):1345-1357. doi:10.1038/s41379-021-00790-1
89. Fox SE, Falgout L, Vander Heide RS. COVID-19 myocarditis: quantitative analysis of the inflammatory infiltrate and a proposed mechanism. *Cardiovasc Pathol*. Sep-Oct 2021;54:107361. doi:10.1016/j.carpath.2021.107361
90. Goldman BI, Choung HY, Sainvil M, Miller CW. The spectrum of macrophage-predominant inflammatory myocardial disease presenting as fulminant heart

failure. *Cardiovasc Pathol*. Mar-Apr 2022;57:107393. doi:10.1016/j.carpath.2021.107393

91. Radovanovic M, Petrovic M, Barsoum MK, et al. Influenza Myopericarditis and Pericarditis: A Literature Review. *J Clin Med*. Jul 15 2022;11(14)doi:10.3390/jcm11144123
92. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol*. Feb 2022;19(2):75-77. doi:10.1038/s41569-021-00662-w
93. Verma AK, Lavine KJ, Lin CY. Myocarditis after Covid-19 mRNA Vaccination. *N Engl J Med*. Sep 30 2021;385(14):1332-1334. doi:10.1056/NEJMc2109975
94. Glass CK, Mitchell RN. Winning the battle, but losing the war: mechanisms and morphology of cancer-therapy-associated cardiovascular toxicity. *Cardiovasc Pathol*. Sep-Oct 2017;30:55-63. doi:10.1016/j.carpath.2017.06.009
95. Thuny F, Naidoo J, Neilan TG. Cardiovascular complications of immune checkpoint inhibitors for cancer. *Eur Heart J*. Nov 7 2022;43(42):4458-4468. doi:10.1093/eurheartj/ehac456
96. 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
97. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol*. Apr 24 2018;71(16):1755-1764. doi:10.1016/j.jacc.2018.02.037
98. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N Engl J Med*. Jan 6 2022;386(1):24-34. doi:10.1056/NEJMoa2109970
99. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med*. Jul 26 1990;323(4):236-41. doi:10.1056/NEJM199007263230405
100. Torre-Amione G, Kapadia S, Lee J, Bies RD, Lebovitz R, Mann DL. Expression and functional significance of tumor necrosis factor receptors in human myocardium. *Circulation*. Sep 15 1995;92(6):1487-93. doi:10.1161/01.cir.92.6.1487
101. Torre-Amione G, Kapadia S, Lee J, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. *Circulation*. Feb 15 1996;93(4):704-11. doi:10.1161/01.cir.93.4.704
102. Bruckner BA, Stetson SJ, Perez-Verdia A, et al. Regression of fibrosis and hypertrophy in failing myocardium following mechanical circulatory support. *J Heart Lung Transplant*. Apr 2001;20(4):457-64. doi:10.1016/s1053-2498(00)00321-1
103. Cordero-Reyes AM, Youker KA, Trevino AR, et al. Full Expression of Cardiomyopathy Is Partly Dependent on B-Cells: A Pathway That Involves Cytokine Activation, Immunoglobulin Deposition, and Activation of Apoptosis. *J Am Heart Assoc*. Jan 14 2016;5(1)doi:10.1161/JAHA.115.002484

104. Hobbs JR, Hugh-Jones K, Barrett AJ, et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet*. Oct 3 1981;2(8249):709-12. doi:10.1016/s0140-6736(81)91046-1
105. Staba SL, Escolar ML, Poe M, et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *N Engl J Med*. May 6 2004;350(19):1960-9. doi:10.1056/NEJMoa032613
106. Gentner B, Tucci F, Galimberti S, et al. Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome. *N Engl J Med*. Nov 18 2021;385(21):1929-1940. doi:10.1056/NEJMoa2106596
107. Birks EJ, Drakos SG, Patel SR, et al. Prospective Multicenter Study of Myocardial Recovery Using Left Ventricular Assist Devices (RESTAGE-HF [Remission from Stage D Heart Failure]): Medium-Term and Primary End Point Results. *Circulation*. Nov 24 2020;142(21):2016-2028. doi:10.1161/CIRCULATIONAHA.120.046415
108. Zimmerman H, Covington D, Smith R, Ihnat C, Barber B, Copeland J. Recovery of dilated cardiomyopathies in infants and children using left ventricular assist devices. *ASAIO J*. Jul-Aug 2010;56(4):364-8. doi:10.1097/MAT.0b013e3181e1d228
109. Jennings DL, Jones MC, Lanfear DE. Assessment of the heart failure pharmacotherapy of patients with continuous flow left-ventricular assist devices. *Int J Artif Organs*. Mar 2012;35(3):177-9. doi:10.5301/ijao.5000068
110. Imamura T, Kinugawa K, Hatano M, et al. Preoperative beta-blocker treatment is a key for deciding left ventricular assist device implantation strategy as a bridge to recovery. *J Artif Organs*. Mar 2014;17(1):23-32. doi:10.1007/s10047-013-0748-7
111. McCullough M, Caraballo C, Ravindra NG, et al. Neurohormonal Blockade and Clinical Outcomes in Patients With Heart Failure Supported by Left Ventricular Assist Devices. *JAMA Cardiol*. Feb 1 2020;5(2):175-182. doi:10.1001/jamacardio.2019.4965
112. Ramzy D, Soltesz E, Anderson M. New Surgical Circulatory Support System Outcomes. *ASAIO J*. Jul 2020;66(7):746-752. doi:10.1097/MAT.0000000000001194
113. Ramzy D, Anderson M, Batsides G, et al. Early Outcomes of the First 200 US Patients Treated with Impella 5.5: A Novel Temporary Left Ventricular Assist Device. *Innovations (Phila)*. Jul-Aug 2021;16(4):365-372. doi:10.1177/15569845211013329
114. Ammirati E, Cipriani M, Moro C, et al. Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis: Multicenter Lombardy Registry. *Circulation*. Sep 11 2018;138(11):1088-1099. doi:10.1161/CIRCULATIONAHA.118.035319
115. Ammirati E, Lupi L, Palazzini M, et al. Prevalence, Characteristics, and Outcomes of COVID-19-Associated Acute Myocarditis. *Circulation*. Apr 12 2022;145(15):1123-1139. doi:10.1161/CIRCULATIONAHA.121.056817

116. Ammirati E, Veronese G, Brambatti M, et al. Fulminant Versus Acute Nonfulminant Myocarditis in Patients With Left Ventricular Systolic Dysfunction. *J Am Coll Cardiol*. Jul 23 2019;74(3):299-311. doi:10.1016/j.jacc.2019.04.063
117. Mirza KK, Szymanski MK, Schmidt T, et al. Prognostic Value of Peak Oxygen Uptake in Patients Supported With Left Ventricular Assist Devices (PRO-VAD). *JACC Heart Fail*. Oct 2021;9(10):758-767. doi:10.1016/j.jchf.2021.05.021
118. Potapov EV, Antonides C, Crespo-Leiro MG, et al. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. *Eur J Cardiothorac Surg*. Aug 1 2019;56(2):230-270. doi:10.1093/ejcts/ezz098
119. Burkhoff D, Topkara VK, Sayer G, Uriel N. Reverse Remodeling With Left Ventricular Assist Devices. *Circ Res*. May 14 2021;128(10):1594-1612. doi:10.1161/CIRCRESAHA.121.318160
120. Stainback RF, Estep JD, Agler DA, et al. Echocardiography in the Management of Patients with Left Ventricular Assist Devices: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. Aug 2015;28(8):853-909. doi:10.1016/j.echo.2015.05.008
121. Topkara VK, Garan AR, Fine B, et al. Myocardial Recovery in Patients Receiving Contemporary Left Ventricular Assist Devices: Results From the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). *Circ Heart Fail*. Jul 2016;9(7)doi:10.1161/CIRCHEARTFAILURE.116.003157
122. Rame JE, Pagani FD, Kiernan MS, et al. Evolution of Late Right Heart Failure With Left Ventricular Assist Devices and Association With Outcomes. *J Am Coll Cardiol*. Dec 7 2021;78(23):2294-2308. doi:10.1016/j.jacc.2021.09.1362
123. Enriquez AD, Calenda B, Gandhi PU, Nair AP, Anyanwu AC, Pinney SP. Clinical impact of atrial fibrillation in patients with the HeartMate II left ventricular assist device. *J Am Coll Cardiol*. Nov 4 2014;64(18):1883-90. doi:10.1016/j.jacc.2014.07.989
124. Yuzefpolskaya M, Uriel N, Chow DS, et al. Prevalence and timing of bend relief disconnection in patients supported by the late version HeartMate II left ventricular assist device. *J Heart Lung Transplant*. Mar 2013;32(3):320-5. doi:10.1016/j.healun.2012.11.016
125. Milwidsky A, Alvarez Villela M, Wiley J, et al. Outflow graft obstruction in patients with the HM 3 LVAD: A percutaneous approach. *Catheter Cardiovasc Interv*. Dec 1 2021;98(7):1383-1390. doi:10.1002/ccd.29785
126. Farber G, Kirov H, Schwan I, et al. Bend relief fenestration might prevent outflow graft obstruction in patients with left ventricular assist device. *Interact Cardiovasc Thorac Surg*. Jul 9 2022;35(2)doi:10.1093/icvts/ivac149
127. Dimitrov K, Kaider A, Angleitner P, et al. Incidence, clinical relevance and therapeutic options for outflow graft stenosis in patients with left ventricular assist devices. *Eur J Cardiothorac Surg*. Feb 18 2022;61(3):716-724. doi:10.1093/ejcts/ezab382
128. Joury A, Patel RAG, Wever-Pinzon J, et al. Cerebral protection during percutaneous intervention for left ventricular assist device outflow graft obstruction. *Catheter Cardiovasc Interv*. Aug 2022;100(2):266-273. doi:10.1002/ccd.30241

129. Brewer JM, Tran A, Yu J, et al. ECMO after cardiac surgery: a single center study on survival and optimizing outcomes. *J Cardiothorac Surg*. Sep 19 2021;16(1):264. doi:10.1186/s13019-021-01638-0
130. Mehra MR, Goldstein DJ, Cleveland JC, et al. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. *JAMA*. Sep 27 2022;328(12):1233-1242. doi:10.1001/jama.2022.16197
131. John R, Kanwar MK, Cleveland JC, Jr., et al. Concurrent valvular procedures during left ventricular assist device implantation and outcomes: A comprehensive analysis of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 trial portfolio. *J Thorac Cardiovasc Surg*. Apr 25 2022;doi:10.1016/j.jtcvs.2022.04.021
132. Uriel N, Milano C, Agarwal R, et al. Incidence and clinical correlates of de-novo aortic regurgitation with a fully magnetically levitated left ventricular assist device: a MOMENTUM 3 trial portfolio analysis. *Eur J Heart Fail*. Feb 2023;25(2):286-294. doi:10.1002/ejhf.2746