Brano Heart Failure Forum Proceeding Paper

Highlights of the 2023 Brano Heart Failure Forum

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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 2023 BHFF forum was held on the 13th thru 15th of September 2023 in Budapest, Hungary. It was attended by over 100 faculty from 16 countries. In addition, participation through online streaming was available. Throughout the forum, 16 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.

Keywords: heart failure, heart transplantation, cardiology
End-stage Heart Failure Treatment Options and Dilemmas

Current Outcomes and Expectations with Heart Transplantation and Mechanical Circulatory Support: Where are the Opportunities?

Presenter James Kirklin

Since 1990, the annual number of heart transplants (HTx) worldwide approaches 500. In the current era, 2-year survival exceeds 80%, with a median survival of 13 years. Since approval by the United States (US) Food and Drug Administration in 2017, the HeartMate 3 (HM3, Abbott Laboratories), a fully magnetically levitated continuous flow left ventricular assist device (LVAD), has rapidly captured > 90% of the durable LVAD (dLVAD) implant volume, with 2-year survival > 80%. In the US, currently 75% of dLVADs are implanted as long-term destination therapy (DT). With DT and HTx, a major opportunity exists to increase the total number of patients with advanced heart failure (HF) who may benefit from extended survival.

However, some aspects of these complex therapies remain challenging. Survival after primary biventricular VAD (BVAD) support is < 60% at 1 year, without improvement in the most recent era. Delayed support of severe right heart failure (RHF) with sequential BVAD has worse outcomes than patients with concurrent BVAD implants. Survival after total artificial heart (TAH) remains < 55% at 1 year, also with no improvement in the recent era. These support types represent < 5% of device implants. With new TAHs and improved biventricular devices in future trials, a major opportunity may emerge to expand the imprint of biventricular support.

Improved survival with dLVADs has created an opportunity to explore the expansion of LVAD therapy in the elderly as an alternative to HTx. Recent studies found that patients > 75 years old are generally selected with fewer comorbidities than younger patients to avoid complications after LVAD implantation. Elderly patients experience marked improvement in both functional capacity and health-related quality of life (HRQOL) after LVAD, similar to younger patients.

Barriers remain in the application of durable devices to the group of patients with ambulatory advanced HF (Interagency Registry for Mechanically Assisted Circulatory Support Profiles 4-7), which comprises < 15% of total implants, unchanged since 2016. Hesitancy to refer such patients hinges on the impact of adverse events (AEs) on survival and HRQOL. However, improvement in some areas (survival, freedom from stroke, gastrointestinal bleeding, and pump thrombus) has been identified with the HM3; however, the rates of device-related infection are similar. New onset RHF at 3, 6, and 12 months is about 5%. Adverse events have a major negative effect on HRQOL in both early and late follow-up. Understanding the impact of AEs on HRQOL may assist shared decision-making regarding LVAD eligibility. With continued reduction of the number and impact of major AEs, the field may experience renewed interest in expanding the imprint of LVADs into ambulatory advanced HF.

Update on New LVADs on the Horizon

TORVAD

Presenter Richard Smalling

The TORVAD (Windmill Cardiovascular Systems, Austin, TX) is unlike any other VAD on the market or in development, offering several unique features and advantages. The TORVAD is
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pulsatile; its rate and rhythm are responsive to simulate natural blood flow; it automatically reacts to physiological demands for flow; and it minimizes blood damage by its gentle pumping action. Pumping is achieved by two rotary pistons that produce positive-displacement flow with low rotational speeds (typically the rotations per minute equals the heart rate). These advantages will likely reduce currently reported AEs associated with continuous flow devices, which include unacceptably high rates of stroke (24%), bleeding (32%), infection (33%), and especially rehospitalization (93%). Reducing AEs could also expand the utilization of VAD technology to a broader patient population with improved HRQOL and patient mobility, allowing more effective treatment in less sick patients. The ability to instantaneously respond to changes in heart rate offers more freedom in the activities of normal daily living, allowing patients to live, not simply survive. These claims have been demonstrated in extensive testing. Benchtop durability experiments for over 20 months and counting have demonstrated device reliability. Benchtop experiments with fresh whole human blood have shown preservation of von Willebrand Factor (vWF), lower hemolysis, and lower platelet activation than continuous flow devices. Acute and chronic animal experiments have shown synchronous pumping, no depletion of vWF, and a thrombo-resistant design. Windmill is actively raising funds to complete preclinical testing and initiate a first-in-human clinical trial.

Cardiac Resynchronization Therapy and Therapeutic Options in Patients with Ventricular Tachycardia

New Results in Cardiac Resynchronization Therapy in Heart Failure

Presenter Annamaria Kosztin

Annually, ~300,000 patients worldwide develop left ventricular (LV) systolic dysfunction due to intraventricular dyssynchrony induced by the right ventricular (RV) pacing, which leads to HF hospitalizations and associated adverse clinical outcomes. Despite this high number, there is a lack of high-quality data from large randomized controlled trials (RCTs) investigating cardiac resynchronization therapy (CRT) upgrades. CRT upgrades are when an extra LV lead is implanted to the previous pacemaker (PM) or implantable cardioverter defibrillator (ICD). Without RCT data, uncertainties remain in everyday clinical practice. The class/level of recommendation for CRT upgrade has been modified several times, demonstrating an unmet need for more robust evidence.

BUDAPEST CRT Upgrade\(^8\) was the first trial to compare the efficacy and safety of a CRT upgrade to ICD alone. The trial enrolled symptomatic HF patients (New York Heart Association class II–IVa) with reduced ejection fraction (≤ 35%), an already implanted PM or ICD, a wide-paced QRS complex (≥ 150 ms), and a high burden of RV pacing (≥ 20%). Patients were randomized to receive a CRT-D upgrade or ICD in a 3:2 ratio. The primary outcome was the composite of HF hospitalization, all-cause mortality, or < 15% reduction of LV end-systolic volume. Secondary outcomes included a composite of HF hospitalization and all-cause mortality and echocardiographic response (ie, change of LV ejection fraction or volumes). Safety outcomes were also assessed.

A total of 360 patients were randomly assigned to receive a CRT-D (n = 215) or an ICD (n = 145) from 17 sites in 7 countries. The mean age was 72.8 years; almost two-thirds of the patients had a PM, and 89% were men. During a median of 12.4 months, the primary outcome occurred in 58/179 (32.4%) patients in the CRT-D arm and 101/128 (78.9%) in the ICD arm.
(adjusted odds ratio = 0.11; 95% confidence interval = 0.06 - 0.19; P < .001). The treatment effect of CRT-D upgrade was homogenous across all prespecified subgroups. In the composite of HF hospitalization and all-cause mortality, CRT-D was superior compared to ICD alone (adjusted hazard ratio = 0.28 [P < .001]). Echocardiographic LV morphological and functional improvement also favored CRT-D, with a difference at 12 months in LV end-diastolic volume of -39.00 mL (P < .001) and a difference at 12 months in LV ejection fraction of 9.76% (P < .001). These changes were correlated with the decreased occurrence of major ventricular arrhythmias (CRT-D arm 1/215 patients [0.5%], ICD arm 21/145 patients [14.5%]). The incidence of procedure- or device-related complications was comparable between the two arms: CRT-D group 25/211 (12.3%) vs. ICD group 11/142 (7.8%).

These findings support that CRT upgrade should be performed immediately without postponing the procedure to a later date to avoid or reduce the risk of further AEs such as mortality, HF hospitalization, or LV remodeling.

Heart Transplantation New Allocation System and Outcomes

Waitlist Outcomes in the New Heart Allocation System Era

_Presenter Maryl R. Johnson_

In October 2018, the US Organ Procurement and Transplantation Network instituted a new priority system for allocating donor hearts based primarily on predicted waitlist mortality. This was done because too many candidates with disparate mortality risks were in the most urgent status in the prior system. The previous policy did not accommodate the increasing use of mechanical circulatory support devices (MCSD), and the number of status exception requests was high. The new allocation policy also included more specific criteria to qualify for priority based on using MCSDs, inotropes, or arrhythmias. Comparing the 4 years before the policy implementation (10/18/2014 – 10/17/2018) to the 4 years following policy implementation (10/18-2018 – 10/17-2022), the following can be concluded:

1) The percentage of patients listed as Status 1, 2, and 3 in the current system was higher than that listed as the equivalent Status 1A in the prior system.

2) In both listed and transplanted candidates, the use of extracorporeal membrane oxygenation and intra-aortic balloon pumps (IABPs) increased, and the use of LVADs decreased.

3) The new status criteria prioritized patients with the highest waitlist mortality in the right sequence, except Status 5 patients, who had higher waitlist mortality than Status 4 patients.

4) The waitlist mortality of patients listed as Status 2 was more like Status 3 patients than that of other categories listed as Status 2.

5) Waiting times were decreased, especially for the higher acuity statuses.

6) Transplant rates (transplants per 100 patient-years) increased.

7) There was no impact on registrations, heart utilization, or 3-year posttransplant survival.
8) Hearts are traveling farther for transplant.

9) A large number of exception requests are still being submitted, especially for Status 2.

Based on this analysis of the New Heart Allocation System, additional modifications are planned. A policy proposal is out for public comment that would require initiation and failure of inotropic therapy before the use of an IABP or MCSD for a candidate to qualify for Status 2. In addition, a system of continuous distribution is currently being developed in which patient characteristics in several categories (medical urgency, posttransplant survival, considerations to decrease biological disadvantages, patient access, and placement efficiency) would be used to define a heart allocation score. It is hoped that a composite of these factors will better prioritize the use of the available donor organs for candidates in need of a HTx.

Heart Transplantation and Durable Left Ventricular Assist Device Therapy in Older Adults

Presenter Francis D. Pagani

In the US, ~6.7 million Americans suffer from HF, with ~335,000 patients experiencing advanced stages of HF (American Heart Association [AHA] Stage D) associated with a 15-20% annual mortality.9,10 While HF afflicts all ages, its prevalence is greatest in older adults ≥ 65 years; the median age of HF diagnosis is 66 years for men and 72 years for women.11-13 Despite being a disease of older adults, advanced surgical therapies, including HTx and implantation of a dLVAD, which offer significant survival benefits and improve HRQOL and functional status, are infrequently used to treat advanced HF in older adults. Therapeutic application of HTx in older adults remains very restricted; only 741 HTxs were performed in 2022 due to donor organ resource limitations and concerns for worse outcomes.14 Older patients have the highest waitlist mortality (11.1 vs. 6.6 deaths/100 patient-years for candidates 18-34 years),15 and the highest 1-year post-HTx mortality (11.8% versus 7.2% for recipients 18-34 years).15 While the median age of HTx recipients is 54 years, only 20% of patients listed for HTx are older adults; this supports the contention that fewer older adults receive the therapeutic benefit of HTx.15 While underuse of HTx in older adults may be rationalized in terms of limited resource allocation, dLVADs are not resource-limited and represent an AHA/American College of Cardiology recommended treatment option for advanced HF16; yet only 76417 adults > 65 years received a dLVAD in 2022, with therapeutic application of dLVADs continuing to decline.18

An approach to reduce the disparity in the treatment of advanced HF for older adults could include greater adoption of dLVAD therapy by demonstrating non-inferior outcomes to HTx. Contemporary dLVAD technology has: 1) achieved equivalent survival to that of HTx for the first 3 years of dLVAD support3; 2) achieved a 5-year survival of 64%17; 3) and significantly reduced rates of AEs.17,19,20 Potential explanations for the restricted use of dLVAD support in older adults may include: 1) lack of data regarding comparative effectiveness to a strategy of HTx listing; 2) lack of provider and patient understanding of contemporary dLVAD outcomes; and 3) potential biases in provider referral.21

The justification for choosing dLVADs over HTx in older adult patients is based on a multifaceted assessment of medical, practical, and ethical factors. The advantages of dLVAD in this population include a more timely intervention and improved survival, functional status, and HRQOL. While HTx remains a valuable option, dLVADs provide a crucial alternative that aligns
with the unique needs and challenges faced by older adult patients with HF. As dLVAD technology advances, the decision-making process for managing HF in older adults will likely become more nuanced and patient-centered.

Hot (Cold) Topics in Heart Transplantation

Warm or Cold: That is the question

Presenter Sandro Sponga

The strategy of donor organ preservation can directly affect HTx outcomes by reducing recipient complications and reconditioning the donor's hearts, thereby expanding the donor pool. Static cold storage is the most widely used donor organ preservation technique, but other approaches are increasingly studied and brought to the field. This study analyzed the outcomes of HTx with regard to graft preservation techniques.

Between 2020 and 2022, 74 patients received HTx with grafts preserved with iced-cold storage (SCS, n = 32), normothermic perfusion with Organ-Care-System (OCS, n = 22), and controlled 4°C hypothermia with Paragonix SherpaPak (SP, n = 20). The three groups were compared for clinical characteristics, results, and histological graft examinations (Table).

**Table. Comparison of graft preservation techniques on heart transplant outcomes**

<table>
<thead>
<tr>
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<th>Iced Cold Storage (SCS)</th>
<th>Normothermic Perfusion with Organ-Care-System (OCS)</th>
<th>Controlled 4°C Hypothermia with Paragonix SherpaPak</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>22</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1 (4%)</td>
<td>3 (14%)</td>
<td>2 (10%)</td>
<td>.65</td>
</tr>
<tr>
<td>Primary graft dysfunction ≥ moderate grade</td>
<td>1 (4%)</td>
<td>2 (9%)</td>
<td>2 (10%)</td>
<td>.33</td>
</tr>
<tr>
<td>1-year overall mortality</td>
<td>1 (4%)</td>
<td>5 (22%)</td>
<td>2 (10%)</td>
<td>.1</td>
</tr>
<tr>
<td>Graft-related 1-year mortality</td>
<td>1 (4%)</td>
<td>3 (13%)</td>
<td>1 (7%)</td>
<td>.21</td>
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Compared to the SCS, OCS and SP patients had a higher IMPACT score (P = .07) and more LVAD support (P = .01). Extended criteria donor rate was similar between groups, while ischemic time was significantly reduced in OCS (P < .001). After preservation and before the implant, grafts preserved with ice were more likely to show edema, while those preserved with normothermic perfusion developed more hemorrhagic lesions.

Controlled hypothermia and normothermic perfusion were used in increasingly complex high-risk scenarios with satisfactory outcomes. These techniques have shown their capabilities to limit ischemic time, leading to less graft damage risk. The preservation technique of the graft could impact the results after HTx regarding the characteristics of the donors and recipients.
Management Following Heart Transplantation

Sodium-glucose Cotransporter 2 Inhibitors: Potential Benefits after Heart Transplant

Presenters Lina Brinker, Konstantinos Sideris, Josef Stehlik

HTx markedly improves survival in advanced HF. However, HTx recipients remain at elevated risk for kidney and cardiovascular (CV) morbidity and mortality. Mitigating the negative effects of these morbidities on long-term survival after HTx is a critical unmet need.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)—novel medications originally designed to treat diabetes (DM)—have pleiotropic mechanisms of action and improve CV and metabolic outcomes for patients with HF and chronic kidney disease (CKD), regardless of DM status. We posit that SGLT2i may offer similar benefits to HTx recipients (Figure).

Figure. Overview of mechanisms by which heart transplant recipients may derive benefit from sodium-glucose cotransporter 2 inhibitors (SGLT2i). Abbreviations: HTx = heart transplant; Na+ = sodium; CNI = calcineurin inhibitors

Metabolic comorbidities are associated with poor outcomes after HTx. DM before and/or after HTx is common and increases the risk of severe kidney dysfunction and mortality. Obesity perpetuates DM, CKD, and cardiac allograft vasculopathy. SGLT2i directly lowers blood glucose levels by inhibiting glucose reabsorption, resulting in glucosuria; additionally, it
improves beta cell function and insulin sensitivity. These combined effects decrease hemoglobin A1c levels by 0.5-1%. SGLT2i also promotes lipolysis and reduces visceral adipose tissue, providing an average weight loss of 1-2 kg.

CKD after HTx is common and is a potent predictor of mortality. Mediated by CV and metabolic comorbidities and augmented by the nephrotoxic effects of calcineurin inhibitors (CNIs), CKD is progressive, and we have no specific treatment. SGLT2i inhibits sodium reabsorption, causing natriuresis, which restores tubuloglomerular feedback and constricts the afferent renal arteriole, reducing the damage incurred by high intraglomerular pressure. SGLT2i acts directly at the cellular level as well, mitigating kidney injury by decreasing reactive oxygen species and interrupting inflammat ory and pro-fibrotic signaling pathways.

Hypertension (HTN) is highly prevalent after HTx, affecting up to 90% of recipients, likely driven by CNI use combined with increased sodium avidity and fluid sensitivity. SGLT2i consistently improves systemic blood pressures—a result of natriuresis, modulation of sympathetic activity, and decreased vessel inflammation. On a microvascular level, SGLT2i might reduce graft vascular loss and decrease the development of diastolic HF.

Anemia is also common in HTx recipients, and persistent anemia is associated with increased mortality. SGLT2i increases erythropoietin and improves anemia, which may contribute to the decrease in CV mortality seen with SGLT2i in large trials.

In addition to addressing multiple high-risk comorbidities, SGLT2i may provide specific benefits to HTx recipients. In experimental models, SGLT2i reversed tacrolimus-mediated kidney injury and pancreatic dysfunction. Clinical data on SGLT2i use in HTx is limited, but small retrospective studies showed that SGLT2i is well-tolerated and improves metabolic markers. In larger retrospective studies of kidney transplant recipients—who have a risk profile similar to HTx recipients—SGLT2i reduced graft failure and all-cause mortality.

Based on their mechanisms of action and existing data, SGLT2i are a promising treatment for HTx. However, prospective studies of SGLT2i to demonstrate safety, tolerability, and efficacy are needed. RCTs of SGLT2i in HTx are currently enrolling in Scandinavia and Australia, and we have proposed a multicenter RCT of US Veterans.

Managing Transplant in the Gene Expression and Cell-Free DNA Era

Presenter Gabriel Sayer

Surveillance for HTx rejection has long relied on the detection of subclinical evidence of rejection that precedes the development of overt graft failure. Molecular and cellular biomarkers have further shifted the paradigm to the detection of inflammatory responses and early signs of cellular injury that may appear before the development of histological rejection. Gene expression profiling (GEP) has been shown to have high negative predictive value, and the incorporation of GEP into surveillance protocols has reduced the number of biopsies that HTx patients need to endure. More recently, the application of donor-derived cell-free DNA (dd-cfDNA) has further advanced the field of noninvasive monitoring for HTx recipients. In the setting of allograft injury, dd-cfDNA can detect small amounts of donor DNA that are released into the bloodstream. Across multiple studies, dd-cfDNA has maintained high negative predictive values for ruling out rejection. When compared to GEP, dd-cfDNA has an improved sensitivity for detecting rejection, including antibody-mediated rejection. Furthermore, emerging research has shown that elevated dd-cfDNA levels are associated with the development of
donor-specific antibodies and cardiac allograft vasculopathy. Most importantly, data suggest that persistently positive dd-cfDNA levels in the absence of biopsy-confirmed rejection are associated with subsequent transplant-related events. Molecular microscopy is an emerging tool that measures gene expression directly in biopsy tissue and can provide complementary information to noninvasive biomarkers for determining the presence of allograft rejection. Future applications of noninvasive biomarkers will include the development of personalized immunosuppression regimens, allowing for a more rapid reduction in immunosuppression levels in selected populations.

The Development of the Transcatheter Aortic Valve Intervention Program in Serbia: Ten-years of Experience

Presenter Milan Nedeljkovic

Aortic stenosis (AS) is the most common valvular disease requiring surgical aortic valve replacement (SAVR) or transcatheter aortic valve intervention (TAVI) in Europe and North America. The first TAVI was performed in 2002 to treat inoperable patients with AS. The initial European Society of Cardiology (ESC) guidelines recommended TAVI for patients with a high risk of SAVR. According to ESC guidelines for the treatment of valvular diseases from 2021, the decision on the treatment modality of AS is defined by the Heart Team, and SAVR is recommended in younger patients with a low risk of surgery (< 75 years; Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM]/EuroScore II < 4%), and TAVI is recommended in elderly patients ≥ 75 years or in patients with high operative risk (STS-PROM/EuroScore II > 8%) or in patients not suitable for surgery. In addition, large RCTs (PARTNER 3, Evolut Low Risk and NOTION studies) showed that TAVI is also safe in patients with a low operative risk (STS-PROM/EuroScore II < 4%), and TAVI is not inferior to SAVR (UK TAVI trial). The first TAVI procedure in the Republic of Serbia was performed on April 22, 2014, during the BASIC 8+ Congress. Between 2014-2023, 444 TAVI procedures were performed in the Republic of Serbia, with an exponential increase in the last 2 years.

References


