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Review

History and Recent Advances in Heart Transplantation: A Narrative Review

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Abstract

Background: Heart transplantation (HTx) has undergone a transformative evolution since the first successful human procedure in 1967. Initially limited by surgical challenges, graft preservation and rejection, the field has advanced through innovations in immunosuppression, mechanical circulatory support (MCS), and donor organ utilization. Despite these achievements, critical challenges persist, including organ shortages, ischemia-reperfusion injury (IRI), and inequities in allocation. Emerging technologies such as normothermic machine perfusion (NMP), donation after circulatory death (DCD) and xenotransplantation aim to expand the donor pool and improve graft viability. **Methods**: This review synthesizes historical and contemporary literature on the evolution of HTx, examining milestones in surgical technique, immunosuppressive strategies and graft preservation. Special emphasis is placed on recent innovations, including ABO-incompatible transplantation, machine perfusion systems, DCD protocols, and xenotransplantation. Comparative analyses of donor policies and the role of MCS as bridge or destination therapy are also considered. **Results**: HTx has progressed from experimental surgery to the gold standard for end-stage heart failure, with survival markedly improved by modern immunosuppression and surgical refinements. However, donor shortage and IRI remain major limitations. Recent advances are reshaping the field: DCD, supported by *ex vivo* and regional perfusion, is expanding the donor pool with comparable outcomes to traditional donation. Machine perfusion technologies enable prolonged preservation, functional assessment of marginal grafts, and potential reduction of IRI. ABO-incompatible transplantation, particularly in infants, has increased donor availability with outcomes comparable to compatible grafts and is now being explored in adults. Xenotransplantation, enabled by CRISPR/Cas9 gene editing of porcine hearts, has reached early human applications, representing a potential paradigm shift despite unresolved immunological and ethical challenges. Meanwhile, durable ventricular assist devices (LVADs) and short-term MCS (e.g., Impella 5.5, ECMO) continue to evolve, serving as effective bridges to transplant or alternatives for non-eligible patients, with survival outcomes approaching transplantation in select groups. **Conclusion**: HTx is entering a new era defined by advanced preservation technologies, expanded donor utilization, and the promise of gene-edited xenografts. While outcomes continue to improve, successful integration of these innovations requires addressing ethical, economic, and equity challenges. Ongoing research, clinical trials, and policy reforms will be critical to fully realize their potential and ensure equitable access for patients with advanced heart failure.

Keywords: heart transplantation; heart failure; immunosuppressive agents; graft survival; organ preservation; donation after cardiac death; machine perfusion; xenotransplantation; ventricular assist devices; extracorporeal membrane oxygenation

History of HTx

The history of heart transplantation is a remarkable journey of medical innovation, perseverance, and scientific advancements. From early experimental procedures to the first successful human heart transplant in 1967, this field has evolved dramatically, saving countless lives worldwide. Heart transplantation (HTx) remains the gold standard for treatment of patients with end-stage heart failure. Advances in immunosuppressive therapy, donor selection, and surgical techniques have significantly improved patient outcomes. Nonetheless, numerous challenges persist -most notably, the shortage of donor organs, ischemia-reperfusion injury (IRI) and limitations of conventional graft preservation methods. In response, a range of innovations has emerged across various domains, including machine perfusion, *ex vivo* preservation systems and xenotransplantation. This review examines these recent developments, with a focus on their clinical relevance and future potential.

Experimental History

Heterotopic Non-Auxiliary Heart Transplantation

The journey started in 1905 with Alexis Carrel and Charles Guthrie at the University of Chicago [1]. During experiments on vascular anastomosis, the researchers performed limb reimplantation and organ transplants, including the heart. In one case, a small dog's heart was transplanted into a larger dog's neck, where it began beating for about an hour after surgery. However, due to a lack of aseptic techniques, thrombi formed, ending the experiment within two hours [2].

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Heterotopic Auxiliary Heart Transplantation

The pioneer of this field was Dr. Demikhov, who performed the first intrathoracic canine heart transplants in the early 1950s [3]. He left the recipient's heart in place yet excluded it from the circulation by ligating the great vessels. Of the 22 canines, one regained consciousness after anesthesia but died 15 hours post-surgery due to superior vena cava thrombosis.

Orthotopic Heart Transplantation

Based on Dr. Demikhov's findings, the next milestone was orthotopic transplantation. In 1953 Neptune *et al*. [4] dedicated themselves to this landmark achievement and initiated the use of topical hypothermia.

Four years later Webb and Howard [5] preserved canine hearts by instilling them with cold potassium citrate before transplanting them. With this finding, they paved the way for long-distance organ procurement.

In 1958 Golberg *et al*. [6] at the University of Maryland performed the first orthotopic heart transplant in dogs, pioneering the left atrial cuff technique, which became the standard for decades. Around the same time, Webb *et al*. [7] used hypothermic preservation, achieving survival times of 30 to 450 minutes. Cass and Brock [8] refined the procedure by introducing right atrial anastomosis, further shaping modern transplantation methods.

Clinical Heart Transplantation

In the late 1950s, Dr. Shumway's team at Stanford standardized the technique, achieving survival of up to 21 days by 1960, but due to ethical and legal concerns, transplant surgeries worldwide faced increased scrutiny in the 1960s. In 1965, Lower *et al*. [9] investigated rejection patterns and their reversal, extending survival to 250 days. By the mid-1960s, the main pitfalls in experimental transplant surgery were addressed to such an extent that Hardy *et al*. [10] felt confident enough to proceed with human heart transplantation. Due to difficulties in finding an appropriate donor, a large chimpanzee heart was used. On January 23, 1964, Dr. Hardy performed the first in-human heart transplant, which turned out to be a xenotransplant [10]. The patient died a few hours after surgery, attributed to unforeseen circulatory overload. On December 3, 1967, Dr. Christiaan Neethling Barnard, performed the first interhuman cardiac transplant [11]. The postoperative course was very promising, but the patient contracted pneumonia and died 18 days later.

On the April 4, 1969, the first left total artificial assist device was implanted by Denton Cooley [12]. The patient was successfully stabilized with this mechanical circulatory support for three days before receiving a transplant. This was the first establishment of a bridge-to-transplant concept.

1983, cyclosporin an immunosuppressant, was granted Food and Drug Administration (FDA) approval in heart transplant surgeries, tackling rejection issues. Cumulative survival rates increased significantly, which led to worldwide gain in acceptance of this procedure.

HTx Technical Aspects

Heterotope Versus Orthotrope

Heterotopic heart transplantation (HHT) is a rare procedure in which recipient's native heart is left in place, and the donor heart is transplanted into the patient's thoracic cavity. One of the key advantages of this approach is that the patient's native heart continues to function alongside the donor's heart, providing additional circulatory support [13]. This protective role was once considered the primary benefit of HHT, but its importance diminished following the introduction of cyclosporins in the 1980s, which significantly improved rejection management.

Another potential benefit of HHT is its utility in cases of donor-recipient size mismatch, in which orthotopic heart transplantation (OHT) may not be feasible. In such scenarios, HHT can be considered to shorten waiting times without significantly increasing morbidity [14].

HHT may also be valuable in pediatric patients with advanced cardiomyopathies, where the scarcity of appropriately sized donor hearts presents a major challenge. In these cases, HHT can serve as a bridge to transplant, reducing waiting time and allowing for left ventricular unloading. This unloading may, in some instances, support the recovery of the native heart's function [15].

Taegtmeyer *et al*. [16] postulated that patients undergoing HHT may experience lower systolic blood pressure compared to those receiving OHT. This observation is based on the hypothesis that the retained native heart valve continues to contribute to the homeostatic regulation of blood pressure.

Despite these potential advantages, HHT is associated with severe complications. The presence of an additional heart in the thoracic cavity can compress the right lung, particularly its lobes, leading to atelectasis, impaired ventilation, and an increased risk of pulmonary infections [17]. In patients with ischemic cardiomyopathy and pre-existing angina pectoris, symptoms may persist even after transplantation, negatively impacting quality of life. Furthermore, progression of native valvular disease can continue postoperatively and may be detected during follow-up evaluations [13].

Patients with dilated cardiomyopathy and an enlarged native heart are at higher risk of postoperative embolic events. To mitigate this risk, anticoagulation therapy is recommended, although this introduces additional challenges and risks following transplantation.

Currently, OHT remains the standard and preferred technique when a suitable donor organ is available. Due to advancements in immunosuppressive therapies and availability of mechanical circulatory support, HHT is now used

infrequently. However, it may still be considered in select cases, depending on patient prognosis and available treatment options.

Biatrial Versus Bicaval

OHT is the established gold standard for patients requiring heart transplantation. Biatrial OHT was introduced by Lower and Shumway [18] in 1960 and is a still widely utilized technique due to its simplicity and thereby inherent reduced ischemia time. However, this technique is known for inferior hemodynamic outcomes as well as higher postoperative arrhythmia rates. In 1990 Yacoub and his group [19] introduced bicaval OHT. This method requires, in addition to the atrial anastomosis, a separate caval anastomosis. Due to the more complex surgical procedure, longer surgery times are expected; however, hemodynamics are better, and arrhythmia rates are lower [20].

A recent systematic review by Zijderhand *et al*. [21] looked at short-term outcomes—such as tricuspid regurgitation, mitral regurgitation, permanent pacemaker implantation rates as well as long term survival of patients undergoing a bicaval versus a biatrial OHT, demonstrating more favorable outcomes in the bicaval group across all aspects.

Standard Immunosuppression

Immunosuppression has been a pivotal factor in enhancing patient outcomes after HTx. Initially, the focus was on high-dose corticosteroids and azathioprine. The introduction of calcineurin inhibitors (CNIs), such as tacrolimus or cyclosporin further improved graft survival rates. Subsequent incorporation of antimetabolites such as mycophenolate mofetil and signal transduction inhibitors like sirolimus and everolimus further optimized the process. The International Society for Heart and Lung Transplantation (ISHLT) currently recommends a triple therapy consisting of Calcineurin Inhibitors, Antimetabolites and Corticosteroids [22]. Strict post-transplant monitoring through endomyocardial biopsies, echocardiography and biomarker assessments aims to detect potential graft rejection at an early stage.

The correct balance between over- and underimmunosuppression is key. Underimmunosuppression can cause rejection, and overimmunosuppression can lead to higher rate of infections, nephrotoxicity as well as malignancies.

New Developments

Breaking Blood-Group Barriers in HTx

ABO incompatibility (ABOi) has traditionally been a contraindication for organ transplantation due to the high risk of hyperacute rejection. This occurs because blood group antigens are not only present on red blood cells but also on endothelial cells of tissues and organs, where they can activate the complement system. This type of immune tolerance begins to develop during infancy [23]. ABOi heart transplantation (ABOi HTx) in adults presents unique immunological challenges, necessitating specialized desensitization protocols to ensure graft survival and reduce the risk of antibody-mediated rejection. Desensitization protocols in adults ABOi HTx are designed to reduce isohemagglutinin titers and lower the risk of antibody-mediated rejection (AMR). These protocols often include plasmapheresis or immunoadsorption to remove circulating anti-ABO antibodies, combined with pharmacologic agents such as intravenous immunoglobulins, rituximab (a monoclonal antibody) and sometimes bortezomib or eculizumab to suppress B-cell and plasma cell activity [24]. The timing and intensity of these therapies vary depending on the patient's antibody levels and sensitization status. Some centers utilize pretransplant desensitization regimes followed by aggressive post-transplant immunosuppression to maintain low antibody levels and prevent AMR.

In 2001 West *et al*. [25] reported a case series involving ten infants who underwent ABOi HTx demonstrating that this procedure can be safely performed in early infancy, prior to the onset of isohemagglutinin production. The aim of this approach is to expand the donor pool, especially within the pediatric population, where high mortality rates are observed among children born with congenital heart diseases on the waiting list. This undertaking is based on the relative immaturity of their immune system, which in turn leads to better acceptance of transplanted organs than at any later time in life. Long-term data have shown comparable outcomes in the ABO and ABOi groups in terms of acute rejection and graft vasculopathy [26]. A retrospective database analysis by Chauhan *et al*. [27] analyzed the data of 1368 infants under one year of age, who underwent ABO-incompatible transplants and found that these transplants did not increase risk of mortality, acute, rejection, or prolonged hospital stay. One, five-, and ten-year survival rates were comparable between ABO-compatible and ABO-incompatible groups (90% vs. 88%, 82% vs. 79%, and 77% vs. 73%, respectively). Further advances in pediatric ABOi and abdominal ABOi transplantations led to the exploration of adult ABO incompatible HTx. An analysis of the ISHLT registry reported no difference in the incidence of death or re-transplantation between ABO and ABOi HTx patients who were transplanted after 2005 [23]. Although ABOi HTx in adults is less common than in pediatric populations, emerging data suggest that with proper desensitization strategies, outcomes can be comparable to those of ABO-compatible transplants [28].

Expanding the Donor Pool: DCD Donation (Donation After Death)

Many strategies have been put in place to keep up with the growing demand of donor hearts. One of these is donation after cardiac death (DCD-HTx). A center-level analysis by Urban *et al*. [29] demonstrated a dramatic increase in transplant rates (from 67 vs. 207 per 100 person-years), doubling the chances of receiving a trans-

plant, without significant differences in waitlist mortality in the USA While transplantations were previously limited to organs from brain-dead donors, DCD donations have become a feasible alternative in recent years. DCD criteria vary across different countries, shaped by legal, ethical and medical frameworks. While the consensus is similar, the exact definitions differ on when and how DCD can occur. The first key distinction in organ donation policies is whether a country follows an opt-in or opt-out system. In opt-out countries—like the UK, Spain, the Netherlands, and Austria—individuals are presumed to consent to organ donation unless they have explicitly declined. In contrast, opt-in countries such as Germany, Canada, and Japan require individuals to actively register their consent. Another important framework is the Maastricht classification for Donation after Circulatory Death (DCD). Categories I and II refer to uncontrolled DCD, typically involving sudden or unexpected deaths. Categories III to V involve controlled DCD, including situations where life support is withdrawn or, in some countries, legally permitted euthanasia [30]. In most countries, a mandatory 'stand-down' period of about five minutes is instituted after circulatory arrest before organ retrieval can begin, to ensure that irreversible death has occurred [30].

DCD donations raise concerns regarding ischemic injury, graft dysfunction, and the long-term risk of allograft vasculopathy. With the introduction of *ex vivo* perfusion (EVP) devices and normothermic regional perfusion (NRP), heart transplantations from donation after circulatory death are increasingly becoming a feasible option [31]. Extraction teams need to be fast to ensure that no lasting ischemic injury is sustained by the donor heart. In the case of EVP, the heart is retrieved and perfused in a machine in a warm beating state. In the case of NRP, after sternotomy, the patient is canulated and connected to an extracorporeal circuit like during regular cardiac surgery. Due to ethical concerns the aortic arch vessels are ligated or transected to prevent any blood flow to the cerebrum. DCD heart transplantation is emerging as a safe, scale and impactful strategy to expand the donor pool—both in the USA and internationally. High-impact studies support its adoption, demonstrating similar patient outcomes to brain-dead donors while significantly increasing the donor pool [32]. Nevertheless, further research is needed to refine protocols for warm ischemia time, donor selection, and recipient matching [33,34].

Pushing Boundaries: Xenotransplant

According to Eurotransplant statistics from 2024, more than 13,000 patients were on the waiting list for an organ in the eight Eurotransplant regions alone. This signifies that human donors alone cannot meet the rising organ demands; hence, alternatives must be found. Due to similarities in size and physiology, pig hearts are considered the most compatible when considering xenotransplants [35]. The main concern in xenotransplantation is a cross-species molecular incompatibility [36]. Advances in gene editing, such as clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9), have enabled the deletion of key antigens that trigger hyperacute rejection, particularly alpha-1,3-galactosyltransferase (GalT). These modifications, along with transgenic expression of human complement-regulatory proteins, have significantly improved graft survival in preclinical models [37]. On January 7, 2022, the world's first successful pig-to-human cardiac xenotransplantation was performed in Baltimore. A 57-year-old patient suffering from end-stage nonischemic cardiomyopathy received a genetically modified pig heart [38]. The patient died two months after the procedure from heart failure. Although there were no direct signs of organ rejection, the multidisciplinary team of physicians assumed that the patient became more vulnerable to organ rejection through his own antibodies, since he could not be prepped with the standard immunosuppression regiment due to his poor clinical state prior to transplant. Furthermore, a latent porcine cytomegalovirus was found in the transplanted heart during autopsy. Lawrence Faucette was the second patient to receive a modified porcine heart in 2023, Maryland. Although the transplant initially showed promising results, he unfortunately passed away six weeks after the transplant due to signs of organ rejection [39]. Xenotransplantation's advancement is hindered by a complex set of scientific, ethical, and practical challenges. The primary obstacle lies in overcoming immunological barriers such as hyperacute rejection and long-term graft survival, despite recent progress with genetically modified pig donors [40]. Ethically, concerns persist around animal welfare, the moral status of genetically engineered animals, and the potential for zoonotic disease transmission, which could become a public health burden [41]. Practically, ensuring rigorous long-term monitoring, developing regulatory frameworks, and achieving public trust remain major hurdles before widespread clinical implementation can occur. Despite these issues, ongoing clinical trials and experimental procedures continue to shape the future of xenotransplantation as a viable solution to end-stage organ failure.

It has been suggested that conducting a greater number of xenotransplantation procedures is essential to establish a learning curve and improve long-term outcomes. While significant challenges remain, xenotransplantation may offer a promising solution to the ongoing organ shortage crisis [42].

Graft Preservation: From Static Cold Storage to Normothermic Perfusion

For decades, static cold storage (SCS) has been the standard method for preserving donor hearts. In this technique, the heart is flushed with a cold cardioplegic solution and placed in an ice bath at 4 °C. While hypothermia slows

Table 1. Graft preservation methods in HTx.

Preservation method	Temperature	System/example	Description
Static Cold Storgage (SCS)	4 °C	Ice box with solution	Heart is stored in hypothermic cardioplegic solution on ice
Hypothermic Machine Perfusion (HMP)	4–10 °C	XVIVO, Paragonix SherpaPak®	Oxygenated perfusion through coronaries, cold
Normothermic Machine Perfusion (NMP)	34–37 °C	OCS-Heart (Transmedics)	Blood based perfusion, monitoring possible, warm
Normothermic Regional Perfusion (NRP)	34–37 °C	*In situ* ECMO based system	Extracorporeal support keeps donors heart viable post-circulatory death
Subnormothermic Perfusion	20–25 °C	Experimental prototypes	Balance metabolism and injury risk, intermediate temperature

OCS, Organ Care System; ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation.

cellular metabolism and delays tissue injury, prolonged ischemic time—typically beyond 4 hours—leads to increased risk of graft dysfunction and post-operative complications [38,43,44]. One type of injury that may occur during long transportation times with prolonged ischemia is ischemia-reperfusion injury (IRI) [45]. This process becomes evident postoperatively, with the patient requiring higher doses of inotropes, pressors and temporary mechanical circulatory support in the form of extracorporeal membrane oxygenation (ECMO) or an intra-aortic balloon pump [46]. To address these limitations, normothermic machine perfusion (NMP) has been introduced as a novel approach that maintains the donor heart in a warm, perfused, and beating state during transport. The Organ Care System (OCS) by TransMedics, for example, allows continuous delivery of oxygen and nutrients while removing waste products. This technology enables real-time functional monitoring, such as lactate clearance, coronary flow, and visual contractility assessment, providing a more accurate evaluation of marginal donor hearts. This prevents ischemic injury and allows the resuscitation and regeneration of marginal hearts to be procured [46]. A single center experience by Russo *et al*. [43] showed that, eight years post-transplant, the overall survival rate was 57.9% in the OCS group compared to 73.7% in the cold storage (CS) group, this difference was not statistically significant. Rates of freedom from cardiac allograft vasculopathy (CAV) were higher in the OCS group (89.5%) than the CS group (67.8%), with a *p*-value of 0.13. Similarly, freedom from non-fatal major adverse cardiac events (NF-MACE) was observed in 89.5% of OCS patients versus 67.5% in CS group. Survival without graft-related death at eight years was identical in both groups at 84.2%. Additionally, no statistically significant differences were found between the groups regarding rejection. An early USA experience reported in JACC found that NRP was associated with superior-short term survival and lower organ rejection rates when compared to direct procurement protocols (DPP) (NRP 1.4% vs DPP 9.6%) [47]. Furthermore, recent literature notes FDA approval of the OCS for DCD hearts and describes *ex vivo* normothermic perfusion's ability to assess and preserve marginal donor hearts-extending the preservation times, minimizing ischemia perfusion injury and increasing geographic transplant reach [46].

The Paragonix SherpaPak® (Getinge, Sweden) Cardiac Transport System preserves the heart in a cold cardioplegic solution. It uses specialized phase-change cold packs to keep the temperature consistently between 4–8 °C. The intended storage time within the SherpaPak is up to 4 hours. The system holds the donor heart in a preservation solution within a sealed, pressure-regulated, rigid container. This ensures uniform cooling, protects against cold-related damage, maintains a stable temperature, and allows for continuous monitoring and data tracking. Other more experimentally used transport systems include XVIVO Heart Perfusion System (XVIVO Perfusion AB, Gothenburg, Sweden), LifeCradle® (TransMedics Group, Inc. Andover, Massachusetts, USA) as well as OrganOx metra (OrganOx Ltd. Oxford, UK). The first two are still undergoing trial phases, and the latter is more focused on liver procurement (See Table 1).

Subzero organ preservation, particulary through supercooling techniques, offers promising advancements over traditional cold storage by potentially enabling long-term preservation without ice formation. Recent developments show that supercooling can successfully preserve organs such as livers, for up to four days, although significiant challenges remain before widespread clinical application becomes feasible.

Preservation Solutions and Metabolic Optimization

To minimize IRI and support cellular health during preservation, various cardioplegic solutions have been developed, each with unique biochemical properties tailored to mitigate cellular stress. These solutions typically include electrolytes for membrane stabilization, buffers to maintain physiological pH, energy substrates to support residual metabolism, and antioxidants to limit oxidative damage [48]. The first widely adopted solution was Euro Collins in the 1960s, followed by the University of Wisconsin (UW) solution, which incorporated impermeants and glutathione

Table 2. Comparison of preservation solutions in HTx.

Solution	Key components	Mechanisms of action	Common use
University of Wisconsin (UW)	Glutathione, adenosine, lactobionate, potassium	Prevents oxidative injury, buffers pH, reduces cellular edema	Solid organ transplant (liver, kidney), occasional heart
Histadine-Tryptophan-Keotgluterate (HTK)	Histidine, tryptophan, ketoglutarate	Buffers pH, reduces free radicals, lowers cellular metabolism	Most widely used for cardiac grafts
Celsior	Glutathione, mannitol, histidine, lactobionate	Antioxidant support, osmotic balance, membrane stabilization	Common in thoracic organ transplants
HTK-N	Dextran 40, potassium, glucose	Enhanced protection against oxidative stress and ischemia	Emerging use in extended preservation
Custodiol N (Modified HTK)	N-acetylhistidine, amino acids, iron chelators	Improved oxidative stress protection, better myocardial function	Experimental use in heart preservation

for enhanced cytoprotection, in the 1980s [49]. Today, over 150 commercially available solutions exist, with Histidine-Tryptophan-Ketoglutarate (HTK), UW and Celsior being the most widely used, each differing in their concentration of histadine, mannitol and other additives [50,51]. Another solution that is not yet frequently used is HTK-N, which is characterized as an organ preservation solution that is electrolyte-balanced, enriched with iron chelators and amino acids, and contains an improved buffering system to enhance its protective effects [52] (See Table 2). New techniques like normothermic perfusion, combined with these solutions, show promise for restoring marginal or previously rejected donor hearts, such as those from donation after circulatory death [46].

Efforts to optimize these solutions have led to the development of perfusion fluids tailored for machine perfusion systems, enhancing myocardial protection during *ex vivo* preservation.

From Pumps to Transplantation: The Evolution of Heart Failure Therapies

While heart transplantation (HTx) remains the gold standard for treating end-stage heart failure, the advent of advanced cardiac resynchronization therapies, including defibrillators and left ventricular assist devices (LVADs), have significantly improved prognosis in recent years [53,54]. LVADs have shown particularly strong outcomes, contributing significantly to improved survival and quality of life in patients not immediately eligible for transplant.

The REMATCH trial was pivotal in demonstrating the clinical benefits of LVADs, showing a one-year survival rate of 52% in the device group compared to 25% in the medical treatment group, although early devices like the HeartMate I were associated with complications such as infections, bleeding, and pump failure, which severely impacted quality of life and long-term outcomes [55,56]. Continuous improvements in LVAD technology have led to newer devices such as the HeartMate 3, a third generation, magnetically levitated system that produces a pseudopulse. The MOMENTUM 3 study demonstrated superior hemocompatibility-related results, including reduced rates of pump thrombosis, decreased stroke and gastrointestinal bleeding rates[57].

Today, modern LVAD systems achieve two-year survival rates comparable to heart transplantation. However, complications persist—most notably driveline infections, often caused by skin flora [58]. The MOMENTUM 3 and ADVANCE trials reported infection rates of 23% and 26.7% within two years post-implantation, respectively, sometimes necessitating antibiotic treatment or surgical intervention [57,59]. Despite this, a five-year overall survival in HeartMate 3 patients reached 58.4%, reinforcing the role of LVADs as a long-term solution for patients who are not transplant candidates [53]. These outcomes, in combination with limited donor organ availability, have established LVADs as a robust alternative to transplantation in carefully selected patients.

Short Term MCS

In acute scenarios, short term MCS options such as extracorporeal membrane oxygenation (ECMO) and the Impella 5.5 provide critical mechanical circulatory support. ECMO, particularly veno-arterial (VA) ECMO is used as a direct bridge to transplant. The United Network for Organ Sharing (UNOS) prioritizes these cases due to the severity of illness [43]. However, outcomes remain poor. For example, Lim *et al*. [60] reported a one-year survival of only 72.9% in ECMO-bridged transplant recipients compared to 95.8% in non-ECMO patients. Post-transplant mortality at 30 days in the ECMO group has been reported as high as 30%, mainly due to multi-organ dysfunction and complications arising from critical illness [61]. Additionally, prolonged ECMO support increases the risk of mortality and adverse outcomes, making it an option typically reserved for cases where other strategies are not feasible [62].

When feasible, transitioning patients from ECMO to durable MCS like an LVAD, once end-organ functions have stabilized, is often preferred. Alternatively, the Impella 5.5 microaxial flow pump has emerged as a promising short-term MCS device. It has been successfully used as a bridge to both transplantation and LVAD implantation. A Mayo

Clinic study reported a one-year post transplant survival rate of 91% in patients supported with the Impella 5.5, with only 4% experiencing rejection requiring further treatment [63,64]. Similarly, Paghdar *et al*. [65] reported a 95% 1-year survival in patients aged 50 and above, who received transplants after axillary Impella 5.5. support, with outcomes exceeding the national averages [66].

Despite classification as a short term MCS (approved for use up to 29 days in the United States of America), clinical experiences have shown that Impella 5.5. can provide stable support for longer durations with fewer complications compared to ECMO. The device allows for patient mobilization, facilitates left ventricular unloading, minimizes left ventricular distention—issues that can be exacerbated by ECMO's afterload-increasing effects. Furthermore, axillary implantation enables outpatient management in some cases, adding to its clinical versatility. While current UNOS listing criteria group it with VA ECMO, emerging data suggest that Impella 5.5. should be considered independently, as its support profile and clinical outcomes more closely align with those of longer-term MCS devices.

In summary, MCS therapies now play a critical and evolving role in the management of advanced heart failure, particularly as bridges to transplantation and as destination therapy. Advances in both durable and short-term devices have expanded the therapeutic arsenal for clinicians, offering tailored support strategies that can improve survival, reduce complications, and extend the transplant window for select patient populations.

Discussion

Heart transplantation operates at the intersection of medical innovation and systemic healthcare challenges, particularly regarding organ allocation, equity in donor selection, and long-term sustainability. In 2023, 4599 heart transplantations were performed in the United States, a record high and more than double the number compared to 2012, driving down adult waitlist mortality to 8.5 deaths per 100 patient-years [67]. Meanwhile, geographic allocation disparities persist: a UNOS registry analysis found that median transplant rates differed by region—0.94 transplants/person-year pre 2018 allocation policy versus 1.51 post policy, yet geography still accounts for roughly 10% of variability in transplant likelihood [68]. Moreover, regional survival rates differed significantly, with Southern US recipients showing lower median post-transplant survival than their counterparts in other regions [69].

In contrast, the Eurotransplant (ET) consortium follows a more inclusive donor-utilization model. A large comparative study revealed that 78% of ET heart transplantations involved donors aged 40 or older with cardiovascular risk factors, whereas the US used such "marginal" donors in only 40% of the cases [70]. In the USA, donor non-acceptance was primarily influenced by age, smoking, and diabetes, while these factors carried less weight in ET. Additionally, obesity and hypertension affected donor rejection rates only in the USA. Had the USA matched ET-level utilization for "mid-quality donors", it could potentially increase transplants by roughly 230 to 930 per year, reducing waitlist deaths and delistings [70].

Equity challenges extend beyond geography. In the USA, racial, socioeconomic and rural disparities profoundly impact access: Black and female patients have lower listing and transplant rates; patients with low socioeconomic status encounter more barriers to immunosuppression and travel for care; and rural residents face longer wait times and reduced access.

Looking at sustainability, advanced therapies such as LVADs incur substantial costs. In the USA, heart failure hospitalizations alone average around $125,000 per patient annually, compared to €18,000 in Europe, constituting between 1–2% of national healthcare spendings [71]. Heart failure care accounts for an estimated 1–2% of national healthcare expenditures in both regions, but the economic burden is felt more acutely in the USA due to higher procedural costs and less centralized cost control. As the demand for advanced heart failure treatments grows, particularly among aging populations, questions arise about the long-term sustainability and equitable access to these high-cost interventions.

In summary, these comparisons illustrate how institutional policies, economic structures, and societal values shape access and outcomes. The ET model exemplifies more liberal donor usage, potentially meeting demands more effectively—but differences in costs, healthcare systems, and regulatory pressures mean solutions cannot simply be copied across regions. For innovations like xenotransplantation and chronic MCS to be truly impactful and equitable, they must be paired with reforms in allocation policy, resource planning, and financial support—especially for underserved populations.

Conclusion

Heart transplantation is entering a new era, driven by breakthroughs in preservation technologies, donor utilization, and genetic engineering. From addressing ischemia-reperfusion injury and extending preservation times with machine perfusion to harnessing the promise of xenotransplantation, these innovations aim to enhance graft viability, expand the donor pool, and improve patient outcomes. Continued research and clinical trials will be essential to validate these technologies and integrate them into standard practice. As these developments mature, they hold the potential to reshape the future of heart transplantation.

Abbreviations

ABOi, ABO Incompatible; AMR, Antibody-Mediated Rejection; CNI, Calcineurin Inhibitors; CAV, Cardiac Allograft Vasculopathy; CS, Cold Storage; DBD, Donation after Brain Death; DCD, Donation

after Cardiac Death; DPP, Direct Procurement Protocol; ECMO, Extracorporeal Membrane Oxygenation; EVP, *Ex Vivo* Perfusion; FDA, Food and Drug Administration; GalT, alpha-1,3-galactosyltransferase; HHT, Heterotopic Heart Transplantation; HTK, Histidine-Tryptophan-Ketoglutarate; HTx, Heart Transplant; IRI, Ischemia-Reperfusion Injury; ISHLT, International Society for Heart and Lung Transplantation; LV, Left Ventricular; LVAD, Left Ventricular Assist Device; NF-MACE, Non-Fatal Major Adverse Cardiac Events; NMP, Normothermic Machine Perfusion; NRP, Normothermic Regional Perfusion; OCS, Organ Care System; OHT, Orthotope Heart Transplantation; SCS, Static Cold Storage; UNOS, United Network for Organ Sharing; USA, United States of America; UWS, University of Wisconsin Solution; VA ECMO, Venoarterial Extracorporeal Membrane Oxygenation.

Author Contributions

DW conceived the study, developed the outline, and supervised the overall project. CZ conducted the literature review, drafted the initial manuscript and prepared the tables. Both authors participated in manuscript revisions, approved the final version for submission and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

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