

## 5. Heart transplantation

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### 5.1 Induction therapy

Bellumkonda L, et al. (2022). The impact of induction therapy on mortality and treated rejection in cardiac transplantation: A retrospective study. J Heart Lung Transplant, S1053-2498(22)00006-7. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35094919/>

- Retrospective analysis using UNOS database to compare outcomes of induction therapy with T cell depleting agents and IL2 receptor antagonists to no induction therapy. Compared to no induction therapy, induction with T cell depleting agent was associated with reduction in risk of treated rejection at 1 year with no effect on mortality. IL2 receptor antagonist was associated with a modest increase in mortality with no impact on risk of rejection.

Bubik RJ, et al. (2021) Malignancy among adult heart transplant recipients following patient-tailored dosing of anti-thymocyte globulin: a retrospective, nested case-control study of individualized dosing. Transpl Int, 34(11):2175-2183. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34411345/>

- Single center, retrospective, matched, nested case-control study to determine the relative risk of rATG exposure with the actual incidence of malignancy post heart transplant.

- 25 out of 126 included patients experienced at least one post-transplant malignancy with an incidence rate of 23.8% at 5 years post-transplant. 14 patients had more than one malignancy. Median rATG cumulative dose in milligrams (mg) was 365 mg in cases and 480 mg in controls (per 100 mg: OR 0.90, 95% CI 0.75–1.08,  $P = 0.28$ ); equivalent of median cumulative rATG dose of 4.7 mg/kg in cases vs. 5.8 mg/kg in controls (per 1 mg/kg: OR 0.92, 95% CI 0.78–1.09,  $P = 0.34$ ). This study did not find a statistically significant correlation between malignancy and cumulative rATG exposure

Kitto B, et al. (2021). Rabbit antithymocyte globulin induction in heart transplant recipients at high risk for rejection. *Ochsner Journal*, 21(2), 133–138. Retrieved from: <https://doi.org/10.31486/toj.20.0024>

- Single-center retrospective cohort study comparing outcomes between high risk adult patients receiving rATG induction vs no induction from 2011–2017. 50 patients were included in the analysis and at one year the composite primary outcome of  $\geq 2R$  rejection, any treated rejection, development of CAV, or graft loss was no different between groups. Infection rate was similar between group, but the rATG group had less prednisone exposure. This study concluded that rATG does not seem to improve allograft outcomes, but can reduce early CCS exposure in patients at high immunologic risk.

Diaz-Castrillon CE, et al. (2021). Induction immunosuppression and renal outcomes in adult heart transplantation. *Journal of Surgical Research*, 259:14–23. Retrieved from: <https://doi.org/10.1016/j.jss.2020.11.021>

- Retrospective analysis using the UNOS database from 2000 to 2018 that evaluated the initiation of de novo dialysis after heart transplantation and the relationship between induction immunosuppression and pre transplant eGFR with post-transplant outcomes. Adjusted multivariable analysis found that induction therapy was associated with de novo dialysis with the most significant effect on patients with eGFR  $\geq 60$ . Overall, the use of induction immunosuppression in orthotopic heart transplantation did not correlate strongly with pre-transplant eGFR and did not mitigate the risk of RRT post-transplant.

Skoric B, et al. (2021). Lower platelet count following rabbit antithymocyte globulin induction is associated with less acute cellular rejection in heart transplant recipients. *Transplantation Proceedings*, 53(1):335–340. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32571710/>

- This was a retrospective single center cohort study that included 156 heart transplant patients who received rATG induction. They found that during the 24 month follow-up period, patients with ACR had significantly higher platelet counts on day 7 and higher ALC on day 14. They concluded that lower platelet count after induction with rATG is associated with less ACR

Watanabe T, et al. (2020). Influence of induction therapy using basiliximab with delayed tacrolimus administration in heart transplant recipients — comparison with standard tacrolimus-based triple immunosuppression. *Circulation Journal*, 84(12), 2212–2223. Retrieved from: <https://doi.org/10.1253/circj.cj-20-0164>

- This retrospective study looked at the influence of induction therapy using basiliximab with delayed FK initiation on outcomes in high-risk heart transplant recipients. Included 86 recipients, 46 of those were included in the induction group (impaired renal function, pre-transplant sensitization, recipient/donor risk factors) and FK administration was delayed. Induction group patients had lower incidence of ACR, but this was not statistically different. Renal function was significantly improved in the induction group, and this group had a significantly increased risk of bacterial or fungal infections. Therefore, basiliximab induction with delayed FK initiation may suppress ACR and improve renal function in high-risk heart transplant recipients.

Nozohoor S, et al. (2020). Induction immunosuppression strategies and long-term outcomes after heart transplantation. *Clinical Transplantation*, 34(7):e13871. Retrieved from: <https://doi.org/10.1111/ctr.13871>

- This study analyzed data from the ISHLF registry for adult heart transplants performed between 2000 and 2013 to look at cumulative all-cause mortality of patients who received no induction, induction with basiliximab, or induction with ATG. Included over 27,000 recipients and found survival was similar in patients treated with no induction compared with ATG, but survival was improved using no induction over basiliximab. Basiliximab was associated with higher risk of graft failure related deaths, and ATG was associated with higher risk of malignancy related deaths.

Truby LK, et al. (2020). Impact of induction immunosuppression on post-transplant outcomes of patients bridged with contemporary left ventricular assist devices. *ASAIO J*, 66(3):261-267. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32101996/>

- Retrospective UNOS database review of patients who had a contemporary, durable, continuous-flow LVAD at the time of heart transplant. Propensity score matching was used to balance characteristics between those who did and did not receive induction therapy. There were no significant differences in graft survival, freedom from hospitalization for rejection, and freedom from hospitalization for infection. However, those who received induction therapy, particularly antithymocyte globulin, experienced a longer time to development of transplant coronary artery disease. Residual bias in patient selection may still exist in this study, but the results suggest that routine induction therapy in patients bridged to heart transplant with contemporary, durable, continuous-flow LVADs may be considered.

Amin AA, et al. (2019). Impact of induction immunosuppression on patient survival in heart transplant recipients treated with tacrolimus and mycophenolic acid in the current allocation era. *Clin Transplant*, 33(8):e13651. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/31230375>

- Heart transplant recipients receiving combination TAC and MPA showed that neither rATG or IL2-RA was associated with survival benefit. Patients receiving rATG showed a significantly higher mortality than patients receiving IL2-RA. Patient receiving IL2-RA showed a trend toward higher associated mortality.

Starling RC, et al. (2019). Accelerated allograft vasculopathy with rituximab after cardiac transplantation. *J Am Coll Cardiol*, 74(1):36-51. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/31272550>

- This study randomized 163 patients to either rituximab 1,000 mg or placebo on days 0 and 12 post transplant to determine if there was a difference in development of CAV. Patients receiving rituximab had significantly higher percent atheroma volume at one year, with similar rates of rejection and mortality.

Gale SE, et al. (2019). Alemtuzumab induction versus conventional immunosuppression in heart transplant recipients. *Journal of Cardiovascular Pharmacology and Therapeutics*, 24(5):435-441. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31035777/>

- Retrospective single-center study comparing 26 patients who met criteria for induction and received alemtuzumab along with reduced tacrolimus, mycophenolate mofetil, and steroids to 26 patients who received standard immunosuppression without induction. At 12 months, alemtuzumab was associated with lower incidences of any rejection of any severity, ACR of any severity, and ACR of grade  $\geq 2$ . No differences were seen in any rejection of grade  $\geq 2$  or AMR. Alemtuzumab was also associated with better preserved renal function in comparison to the group without induction. No differences were seen between groups in neutropenia requiring G-CSF or infections.

Jarmi T, et al. (2018). Outcomes of induction therapy with rabbit anti-thymocyte globulin in heart transplant recipients: a single center retrospective cohort study. *Ann Transplant*, 19 (23): 422-426. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29915167>

- Induction with rATG added no additional survival benefit in heart transplant recipients. Patients not receiving induction therapy were found to have higher life expectancy at both 5 and 10 years post induction.

Briasoulis A, et al. (2018). Induction immunosuppressive therapy in cardiac transplantation: a systematic review and meta-analysis. *Heart Fail Rev*, 23 (5): 641-649. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29532201>.

- Patients receiving induction therapy were found to have similar risk of moderate-to-severe rejection, all-cause death, infection, and cancer than patients that did not receive induction therapy. Patients receiving IL2-RA was associated with a significantly higher risk of moderate-to-severe rejection than patients receiving rATG with similar risk of death, infections, and cancer.

Kittipibul V, et al. (2017). Low-dose basiliximab induction therapy in heart transplantation. *Clinical Transplantation*, 31:e13132. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28990220>.

- The utilization of low-dose de novo basiliximab for induction therapy in heart transplant recipients was shown to have favorable efficacy and safety outcomes. The use of calcineurin inhibitor (CNI) initiation in a low-risk population could be safely delayed using the strategy of modified low-dose post-operative basiliximab. Early corticosteroid wean was also found to be favorable with low-dose basiliximab use but with a higher CNI level and higher doses of mycophenolate.

Ruan V, et al. (2017). Use of anti-thymocyte globulin for induction therapy in cardiac transplantation: a review. *Transplant Proc*, 49(2):253-259. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28219580>

- Use of Anti-thymocyte Globulin for induction therapy in cardiac transplant review article

Aliabadi AZ, et al. (2016). Impact of rabbit antithymocyte globulin dose on long-term outcomes in heart transplant patients. *Transplantation*, 100(3):685-93. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26457604/>

- This retrospective data suggest that a cumulative rATG dose of 4.5 to 7.5 mg/kg for induction may offer a better risk-benefit ratio than lower or higher doses, with acceptable rates of infection and posttransplant malignancy. Prospective trials are needed.

Azarbal B, et al. (2016). Induction therapy with antithymocyte globulin in patients undergoing cardiac transplantation is associated with decreased coronary plaque progression as assessed by intravascular ultrasound. *Circ Heart Fail*, 9(1). Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26747860/>

- Induction therapy with ATG is associated with reduced first-year coronary plaque progression as assessed by IVUS, despite an increased prevalence of sensitized patients with a trend toward more rejection.

Arman D, et al. (2016). Do prior driveline infections increase the risk of infection in heart transplant patients treated with rabbit antithymocyte globulin induction therapy? *Transplant Proc*, 48(10):3393-3396. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27931587>

- The use of ATG induction in patients with prior DLIs did not seem to increase the risk for posttransplant infection (eg, sternal wound infection). ATG induction can therefore be safely used in this population.

Ansari D, et al. (2015). Induction with anti-thymocyte globulin in heart transplantation is associated with better long-term survival compared with basiliximab. *J Heart Lung Transplant*, 34(10):1283-1291.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26087667/>

- A total of 9,324 transplantations performed between 2000 and 2011 whose recipients received ATG (n = 6,144) or BAS (n = 3,180). One-year survival was similar for both groups, 90% vs 91% (p = 0.858). However, use of BAS was associated with poorer long-term survival compared with ATG at 5 years (77% vs 82%, p = 0.005) and at 10 years (64% vs 67%, p = 0.007). In multivariable Cox model, use of BAS remained associated with increased mortality over a median follow-up of 3.0 years (range, 0-12 years), with a hazard ratio of 1.22 (95% confidence interval, 1.09-1.37; p < 0.001). The use of ATG rather than BAS as induction therapy appears to be associated with better long-term survival. A prospective study is necessary to confirm these findings.

Whitson BA, et al. (2015). Impact of induction immunosuppression on survival in heart transplant recipients: a contemporary analysis of agents. *Clin Transplant*, 29(1):9-17. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/25284138/>

- In a contemporary analysis of heart transplant recipients, an overall analysis of induction agents does not appear to impact survival, as compared to no induction immunosuppression. While ALG/ATG/thymoglobulin appeared to have a beneficial effect on survival compared to IL-2Rab in the univariable model, this difference was no longer statistically significant once we adjusted for clinically relevant covariates.

Zuckermann A, et al. (2015). Thymoglobulin induction in heart transplantation: patient selection and implications for maintenance immunosuppression. *Transpl Int*, 28(3):259-69. Retrieved at:

<https://pubmed.ncbi.nlm.nih.gov/25363471/>

- Experts from Germany, Austria, and Switzerland convened to identify indications for rATG induction in heart transplantation and to develop an algorithm for its use based on patient characteristics.

Penninga L, et al. (2013). Immunosuppressive T-cell antibody induction for heart transplant recipients. *Cochrane Database Systematic Reviews*, 12: CD008842. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/24297433>

- This review included 22 RCTs evaluating the use of antibody induction for heart transplant recipients. Acute rejection occurred less frequently with IL2-RA compared to no induction as well as with polyclonal antibody induction compared to IL2-RA and no significant differences regarding mortality, infection, or CAV, cancer or adverse events were detected. However, all included studies were thought to have a high risk of bias and no clear indication of benefit or harm associated with antibody induction could be demonstrated by this review.

Goland S, et al. (2008). Induction therapy with thymoglobulin after heart transplantation: impact of therapy duration on lymphocyte depletion and recovery, rejection, and cytomegalovirus infection rates. *Journal of heart and lung transplantation*, 27: 1115-1121. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/18926403>

- rATG induction consisting of 1.5 mg/kg doses given for five days was compared to a seven day course. Patients receiving the longer induction regimen experienced significantly less acute rejection ( $\geq 1B$ ) at one year without an increase in CMV or bacterial infections.

Carrier M, et al. (2007). Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. *Journal of Heart and Lung Transplantation*, 26: 258-263. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17346628>

- Patients receiving rATG induction experienced less acute rejection at six months than those receiving basiliximab. Non-inferiority of basiliximab was not demonstrated in this investigation.

Mattei MF, et al. (2007). Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. *Journal of Heart and Lung Transplantation*, 26: 693-699. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17613399>

- Prospective, randomized, multi-center comparison of basiliximab and rATG. The incidences of the composite safety end-point (serum sickness, fever, cutaneous rash, anaphylaxis, infection, thrombocytopenia, leukopenia and PTLs) and death due to infection were significantly less in the basiliximab group. No differences in the composite efficacy endpoint (death, graft loss, acute rejection > 1B, acute rejection associated with hemodynamic compromise or treated with antibody therapy, loss to follow up) were observed.

Lindenfeld J, et al (2004). Drug therapy in the heart transplant recipient part i: cardiac rejection and immunosuppressive drugs. *Circulation*, 110: 3734-3740. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15596559>

- First article in a four-part series reviewing medication management for heart transplant recipients. This one focuses on rejection and induction agents.

Cantarovich M, et al. (2004). Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. *Transplantation*, 78: 779-781. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15371689>

- Patients experiencing post-operative renal dysfunction received rATG induction with delayed initiation of cyclosporine. Compared to controls that received cyclosporine beginning on POD2, no significant differences in acute rejection or patient survival were observed.

## **5.2 Maintenance therapy**

### **5.2.1 Calcineurin Inhibitors**

Nanni AN, et al. (2021). Association of tacrolimus time-to-therapeutic range on renal dysfunction and acute cellular rejection after orthotopic heart transplantation in a high use basiliximab population. *Clin Transplant*, e14542. Retrieved from: <https://doi.org/10.1111/ctr.14542>

- Single-center retrospective cohort study in the US from July 2013 to April 2020.
- 46.6% of patients in the study population developed new renal dysfunction after tacrolimus was initiated. Patients who developed new renal dysfunction had a shorter time from transplant to time-to-tacrolimus (TTT) than those who did not develop renal dysfunction (11.6 vs. 13.0 days,  $p = 0.07$ ). However, suprathreshold tacrolimus levels occurred more frequently in the patients who developed new renal dysfunction (56% vs. 39.2%,  $p = 0.01$ ).
- Acute cellular rejection (ACR) occurred in 36.9% of patients within 30 days after OHT. There was no significant difference in TTT between the patients who developed ACR and those who did not (11.1 vs. 10.8 days,  $p = 0.638$ ).

Shiraishi Y, et al. (2020). Impact of tacrolimus versus cyclosporin A on renal function during the first year after heart transplant. *ESC Heart Failure*, 7(4), 1842–1849. Retrieved from: <https://doi.org/10.1002/ehf2.12749>

- This was a retrospective study looking at 72 patients receiving de novo heart transplants at a single center to assess FK vs CsA with clinical outcomes with a focus on nephrotoxicity. In the first year post transplant, 59% of patients in the FK group switched mycophenolate to everolimus, and only 48% in the CsA group switched. There were no differences in renal function or graft rejection within 1 year post transplant between the FK and CsA groups. This study concluded that irrespective of everolimus use with low-dose CNIs, there were no differences in renal function as well as graft rejection during the first year after HTx between HTx recipients who received TAC or CsA.

Guethoff S, et al. (2013). Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine a in combination with mycophenolate mofetil after heart transplantation. *Transplantation*, 95: 629-634. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23423270>

- Freedom from acute rejection was significantly greater at 1, 5 and 10 years for patients receiving tacrolimus-based maintenance immunosuppression. Freedom from CAV was also increased for the tacrolimus group compared to those receiving cyclosporine. No significant differences in patient survival at 1, 5, or 10 years were observed.

Patel JK, et al. (2007). Tacrolimus in heart transplant recipients: An overview. *Biodrugs*, 21:139-143. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17516709>

- Review of investigations comparing tacrolimus to cyclosporine for cardiac transplantation.

Grimm M, et al. (2006). Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients--a large European trial. *American Journal of Transplantation*, 6(6):1387-1397. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16686762>

- Incidence of BPAR  $\geq$  1B and 3A at six months was significantly decreased for patients receiving tacrolimus compared to cyclosporine. TAC-treated patients also developed significantly more NODAT, but less hyperlipidemia and HTN.

Kobashigawa JA, et al. (2006). Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. *American Journal of Transplantation*, 6:1377-1386. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16686761>

- No significant difference in the primary endpoint of grade 3A or greater rejection or rejection associated with hemodynamic compromise was detected. However, significant differences in any treated rejection, median serum creatinine and triglycerides occurred and favored the combination of tacrolimus and MMF.

### 5.2.2 **Antiproliferatives**

Alam A, et al. (2021). Impact of risk-stratified mycophenolate dosing in heart transplantation. *Clinical Transplantation*. Published. Retrieved from: <https://doi.org/10.1111/ctr.14445>

- This was a retrospective single-center study that analyzed 140 consecutive heart transplant patients who were initiated on a risk-stratified MMF protocol post-transplant. The study concluded that the composite rate of BPAR, graft loss, or mortality at 1-year post-transplantation was similar between the two groups. Incidence of neutropenia, thrombocytopenia, infection, cardiac allograft vasculopathy, or acute kidney injury by 1-year also showed similar results between the two groups. This study concluded that risk-stratification of MMF dosing appears to be a safe and effective strategy after heart transplantation.

Woillard JB, et al. (2015). Mycophenolic mofetil optimized pharmacokinetic modelling, and exposure-effect associations in adult heart transplant recipients. *Pharmacol Res*, 99:308-15. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26192348/>

- MPA measured AUC adjusted on CNI exposure was significantly associated with rejection (per unit increase: HR [95% CI]=0.97 [0.95-0.99], p=0.0122), while no effect was shown for adverse events attributable to MMF. An AUC threshold of 50 mg×h/L was proposed (sensitivity=77%, specificity=25%) beyond which the risk of rejection was significantly increased (low vs. high: HR=3.48 [1.21-10.0], p=0.0204).

Eisen HJ, et al. (2005). Three-Year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. *Journal of Heart and Lung Transplantation*, 24:517-525. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15896747>

- Patients receiving AZA were retransplanted or died more frequently and had a shorter time to retransplantation or death than the MMF group. MMF-treated patients also had a smaller change in mean maximal intimal thickness compared to AZA (P = 0.056).

Kabashigawa J, et al. (2005). Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. *Transplantation*, 80:S235-S243. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16251856>

- Review summarizing MMF efficacy studies as well as use in pediatric heart transplantation, coronary allograft vasculopathy and therapeutic drug monitoring.

Kobashigawa J, et al. (1998). A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. *Transplantation*, 66:507-515. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/9734496>

- Rejection that required treatment as well as mortality at one year were significantly reduced in the MMF group. MMF-treated patients did experience more opportunistic infections, predominately HSV.

### **5.2.3 Corticosteroids**

Elboudwarej O, et al. (2017). Corticosteroid wean after heart transplantation-Is there a risk for antibody formation? *Clin Transplant*, 31(4). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28135788>

- Few patients successfully weaned off prednisone after heart transplant develop de novo circulating antibodies but are not at increased risk for developing rejection.

### **5.2.4 Mammalian target of rapamycin (mTOR) inhibitors**

Asleh R, et al. (2022). Sirolimus-Based immunosuppression is associated with decreased incidence of post-transplant lymphoproliferative disorder after heart transplantation: a double-center study. *J Clin Med*, 11(2):322. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35054016/>

- A retrospective review comparing risk of PTLD in sirolimus-based to calcineurin-inhibitor based immunosuppressive regimens. EBV mismatch was strongly associated with increased risk of PTLD (p<0.001), and conversion to sirolimus was protective against development of PTLD (p=0.02) even after adjusting for EBV mismatch (p=0.006).

Asleh R, et al. (2021). Effects of mTOR inhibitor-related proteinuria on progression of cardiac allograft vasculopathy and outcomes among heart transplant recipients. *Am J Transplant*, 21(2):626-635. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32558174/>



- Single center, non-randomized, retrospective cohort performed in the United States from 1994 to 2016. The aim of this study was to determine if conversion to sirolimus-related proteinuria led to progression of cardiac allograft vasculopathy (CAV). There were 137 patients included in the study analysis.
- Of the 137 patients in the study, 36 developed proteinuria at a median of 0.87 years after transplant. The proteinuria group had a significant increase in plaque index (PI%) from baseline compared to the non-proteinuria group (31.6 vs. 26.6,  $p = 0.0002$ ). The proteinuria group also had significantly more severe CAV (grade 0 27.8%, grade 1 61.1%, grade 2 8.3%, grade 3 2.8%) compared to the non-proteinuria group (grade 0 47.5%, grade 1 50.5%, grade 2 1.0% grade 3 1.0%) ( $p = 0.037$ ).
- Of the 17 deaths in the entire study group, 27.8% occurred in the proteinuria group and 6.9% occurred in the non-proteinuria group. 4 deaths occurred due to advanced CAV (30% in the proteinuria group and 14.3% in the non-proteinuria group). Proteinuria after starting sirolimus was associated with increased all-cause mortality compared to the non-proteinuria group for both unadjusted and adjusted analyses ( $p = 0.021$  and  $p = 0.01$ , respectively).

Eisen HJ. (2021). CAVEAT mTOR: You've heard about the benefits of using mTOR inhibitors, here are some of the risks. *Am J Transplant*, 21(2):449-450. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/32715588/>

- Review article discussing the adverse effects of mTOR inhibitors in patients who have received a cardiac transplant.

Sallam K, et al. (2021). Sirolimus adverse event profile in a non-clinical trial cohort of heart transplantation patients. *Annals of Transplantation*, 26:e923536. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/33462174/>

- This study was a retrospective chart review of 221 adult heart transplant recipients who received either sirolimus or MMF as part of their immunosuppression regimen to determine differences in ADEs. There was a statistically significant difference in rates of ADEs with 71% of patients in the sirolimus arm as compared to 40% in the MMF arm. Sirolimus had a higher instance of elevated triglycerides, LLE, and oral ulcerations and was discontinued in 22% of patients.

Anthony C, et al. (2021). Everolimus for the prevention of calcineurin-inhibitor-induced left ventricular hypertrophy after heart transplantation (RADTAC Study). *JACC: Heart Failure*, 9(4), 301–313. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33795116/>

- Prospective, randomized, open-label study in which OHT recipients were randomized at 12 weeks post transplant to low-dose everolimus and FK or standard dose FK group (both groups received MMF and prednisone). The primary endpoint of LVH out of the 40 included patients was significantly lower than the standard dose FK group. There were also significant differences in function and fibrosis which were higher in the low dose everolimus group. There were no differences in blood pressure, renal function, rejection, or infections. This study concluded that low dose everolimus with FK compared with standard dose FK safely attenuates LVH in the first year after OHT with an observed reduction in fibrosis and improvement in myocardial strain.

Acquaro M, et al. (2020). Long-term effects of the replacement of calcineurin inhibitors with everolimus and mycophenolate in patients with calcineurin inhibitor-related nephrotoxicity. *Transplantation Proceedings*. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32113691/>

- Retrospective observational study of 41 patients with renal impairment (eGFR <60 mL/min/1.73 m<sup>2</sup>) for at least 3 months on CNI therapy who had CNI replaced with everolimus. Mean time from heart transplant at conversion was 12 years. Renal function tended to worsen prior to conversion

of CNI to everolimus and tended to stabilize after conversion. While differences between patients who had improvement in renal function and patients who didn't were not significant, the group that saw improvement was characterized by less advanced age and a shorter time from heart transplant. One patient experienced acute late rejection and 3 patients developed chronic rejection.

Gustafsson F, et al. (2020). Everolimus initiation with early calcineurin inhibitor withdrawal in de novo heart transplant recipients: long-term follow-up from the randomized SCHEDULE study. *Transplantation*, 104(1):154-164. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/30893292/>

- In the SCHEDULE trial, heart transplant recipients were randomized to everolimus with reduced-exposure calcineurin inhibitor to weeks 7-11 after transplant, followed by increased everolimus exposure with cyclosporine withdrawal or standard-exposure cyclosporine. After the core 12 month study, immunosuppression was according to the investigator's preference. At 5-7 years post-transplant, renal function continued to be better and CAV continued to be less common in the everolimus group. With regard to BPAR, while there were no events in the everolimus group between the year 3 visit and the 5-7 year visit and the difference between groups in BPAR from time of transplantation to the 5-7 year visit was not significant, there were more treated BPAR events in the everolimus group from time of transplantation to the 5-7 year visit. Graft dimensions and function were similar between groups.

Barten MJ, et al. (2019). Comparing everolimus-based immunosuppression with reduction or withdrawal of calcineurin inhibitor reduction from 6 months after heart transplantation: The randomized MANDELA study. *Am J Transplant*, 19:3006-3017.

- Heart transplant recipients were randomized at month 6 post-transplant to either convert to CNI-free immunosuppression with everolimus and MPA or to continue reduced-exposure CNI with concomitant everolimus. Target everolimus troughs were 5-10 ng/mL for both groups. The CNI-free regimen was associated with better renal function but more BPAR. Notably, 6 of 15 BPAR episodes in the CNI-free group occurred with everolimus concentration <5 ng/mL.

Saber-Moghaddam N, et al. (2019). The change of immunosuppressive regimen from calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors and its effects on malignancy following heart transplantation. *Int Immunopharmacol*, 69:150-158. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30711744>

- Patients converted from CNI to mTOR post-heart transplantation showed a reduction in the development of malignancy and an overall reduction in nephrotoxicity vs patients remaining on a CNI based regimen. The conversion to mTOR from CNI was found to be safe with an overall reduction in all-cause mortality.

Asleh R, et al. (2018). Long-term sirolimus for primary immunosuppression in heart transplant recipients. *J Am Coll Cardiol*, 71(6):636-650. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29420960>.

- Patients that were converted to sirolimus from CNI vs CNI alone experienced a significant attenuation in progression of cardiac allograft vasculopathy (CAV) and reduction in all-cause mortality. Patients also experienced a lower incidence of CAV related events when switched to sirolimus vs. CNI alone.

Hu YN, et al. (2017). High-dose calcineurin inhibitor-free everolimus as a maintenance regimen for heart transplantation may be a risk factor for pneumocystis pneumonia. *Transpl Infect Dis*, 19(4). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28425200>

- In a retrospective review, heart transplant recipients receiving tacrolimus vs. conversion to tacrolimus were found to have non-significant differences in survival rate, rejection rate, and infections except for PJP. A total of 6 patients were diagnosed with PJP in the everolimus conversion group versus the 0 in the control group indicating a potential for higher incidence of PJP with everolimus conversion.

Nelson LM, et al. (2017). Effect of calcineurin inhibitor-free, everolimus-based immunosuppressive regimen on albuminuria and glomerular filtration rate after heart transplantation. *Transplantation*, 101(11):2793-2800. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28230646>.

- Patients receiving everolimus vs standard CNI immunosuppression were found to have a significantly higher eGFR at both 1 and 3 years' post-transplantation but a higher urine albumin/creatinine ratio (UACR) than those receiving standard CNI immunotherapy.

Simha V, et al. (2017). Sirolimus therapy is associated with elevation in circulating pcsk9 levels in cardiac transplant patients. *J Cardiovasc Transl Res*, 10(1):9-15. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1007%2Fs12265-016-9719-8>

- Sirolimus used in transplantation is often associated with hypercholesterolemia. We measured serum lipid and PCSK9 levels in 51 heart transplant recipients who had their immunosuppressive therapy switched from calcineurin inhibitors to sirolimus. The switch resulted in a 23% increase in LDL cholesterol, and 46% increase in triglycerides and PCSK9 levels increased from  $316 \pm 105$  ng/mL to  $343 \pm 107$  ng/mL ( $p = 0.04$ ), however the change in PCSK9 levels did not correlate with an increase in lipid levels ( $p = 0.2$ ). To investigate the mechanism for the variability in the change in PCSK9 levels, lymphoblastoid cell lines were incubated with both sirolimus and everolimus, resulting in a 2-3 fold increase in PCSK9 expression and protein levels in mTOR inhibitor sensitive but not in mTOR inhibitor resistant cell lines. This first in human study demonstrates that sirolimus therapy is associated with elevation in PCSK9 levels which is not associated with sirolimus-induced hypercholesterolemia.

Van Keer J, et al. (2017). The CECARI study: Everolimus (Certican®) initiation and calcineurin inhibitor withdrawal in maintenance heart transplant recipients with renal insufficiency: a multicenter, randomized trial. *J Transplant*. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28316834>

- Heart transplant recipients with baseline renal insufficiency randomized to start everolimus with CNI withdrawal or continuation of CNI did not show a significant change in measured glomerular filtration rate (mGFR) from baseline to year 3 post randomization. No difference was found between all-cause mortality, major cardiovascular events, or treated acute rejection between the two groups.

Andreassen AK, et al. (2016). Everolimus initiation with early calcineurin inhibitor withdrawal in de novo heart transplant recipients: three-year results from the randomized SCHEDULE study. *Am J Transplant*, 16(4):1238-47. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26820618/>

- In a randomized, open-label trial, de novo heart transplant recipients were randomized to everolimus with reduced-exposure calcineurin inhibitor to weeks 7-11 after transplant, followed by increased everolimus exposure with cyclosporine withdrawal or standard-exposure cyclosporine. Early CNI withdrawal after heart transplantation supported by everolimus, mycophenolic acid and steroids with lymphocyte-depleting induction was shown to be safe at intermediate follow-up. This regimen, used selectively, may offer adequate immunosuppressive potency with a sustained renal advantage, however, at the risk of increased biopsy proven acute rejection.

Mirza K, et al. (2016). Effect of everolimus initiation and early calcineurin inhibitor withdrawal on myocardial FOXP3+ regulatory T cells in heart transplantation. *Transpl Immunol*, 38:75-77. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/27260644/>

- Everolimus treatment combined with early CNI elimination is associated with increased densities of Tregs 12-months post-HTx compared to patients receiving CNI based regimen. Furthermore, the density of myocardial FoxP3+ cells early after transplantation appears to predict at least one measure of CAV burden after one year.

Lesche D, et al. (2015). Influence of CYP3A5 genetic variation on everolimus maintenance dosing after cardiac transplantation. *Clin Transplant*, 29(12):1213-20. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26458301/>

- Everolimus pharmacokinetics in HTx recipients is highly variable. This preliminary data on patients on a CNI-free therapy regimen suggest that CYP3A5 genetic variation may contribute to this variability.

Qiu Y, et al. (2015). Conversion from calcineurin inhibitors to mammalian target-of-rapamycin inhibitors in heart transplant recipients: a meta-analysis of randomized controlled trials. *Transplant Proc*, 47(10):2952-6. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26707320/>

- Conversion from CNI to mTORi therapy may improve the renal function in HTRs, but the patients may suffer from a high incidence of mTORi-associated adverse events. Therefore, conversion to mTORi must be carefully assessed for the benefits and risks.

Fuchs U, et al. (2012). Efficacy and safety of low-dose everolimus as maintenance immunosuppression in cardiac transplant recipients. *Journal of Transplantation*, Article ID 976921. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22577516>

- Everolimus 0.75 mg BID targeting trough levels of 5-8 mcg/L was compared to 0.5 mg BID targeting levels of 3-5 mcg/L and no significant difference with respect to the primary composite endpoint including death, rejection, and discontinuation of everolimus was detected.

Topilsky Y, et al. (2012). Sirolimus as primary immunosuppression attenuates allograft vasculopathy with improved late survival and decreased cardiac events after cardiac transplantation. *Circulation*, 125:708-720. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22207715>

- Retrospective evaluation of converting CNI to sirolimus-based maintenance immunosuppression. Plaque index progression, vascular remodeling, freedom for cardiac events and patient survival were all improved with conversion to sirolimus.

Eisen HJ, et al. (2003). Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *New England Journal of Medicine*, 349: 847-858. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/12944570>

- Randomized, double-blind comparison of 1.5 and 3 mg of everolimus and azathioprine in combination with cyclosporine and steroids. Patients receiving either everolimus dose experienced significantly less vasculopathy, composite efficacy endpoint (death, graft loss or retransplantation, loss to follow-up, biopsy-proven acute rejection of grade 3A, or rejection with hemodynamic compromise) and CMV infection.

### 5.2.5 **Belatacept**

Launay M, et al. (2019). Belatacept-based immunosuppression: a calcineurin inhibitor sparing regimen in heart transplant recipients. *Am J Transplant*, 20(2):553-563. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/31452337>

- Belatacept was initiated in the first three months after transplantation in 40 patients, including multiorgan transplant patients to preserve renal function. 76% of cases discontinued their CNI, and GFR improved within one month. 16 patients were discontinued due to GFR recovery (n = 4), DSA no longer detectable (n = 1), compliance issues (n = 3), poor venous access (n = 2), multiple infections (n = 1), 1 death (fungal lung infection), and treatment failure (n = 4).

Ensor CR, et al. (2018). Belatacept for maintenance immunosuppression in cardiothoracic transplantation: the potential frontier. *Clin Transplant*, 32(10). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30058177>

- This is a review article listing the potential benefits of belatacept utilization as maintenance immunosuppression in heart transplantation. Proposed benefits include cardiovascular, metabolic, and neurologic tolerability with lower utilization of calcineurin inhibitors which may prevent nephrotoxicity.

### 5.2.6 Other/General/Review Articles

Oreschak K, et al. (2021). Variants in mycophenolate and CMV antiviral drug pharmacokinetic and pharmacodynamic genes and leukopenia in heart transplant recipients. *The Journal of Heart and Lung Transplantation*, 40(9), 917–925. Retrieved from: <https://doi.org/10.1016/j.healun.2021.05.020>

- This was a retrospective analysis of 148 heart transplant patients who received mycophenolate and an antiviral against CMV to determine the relationship between SNPs in mycophenolate and CMV antiviral drug PK/PD genes and drug-induced leukopenia. Drug induced leukopenia occurred in ~20% of patients with the a specific HNF1A rs1169288 polymorphism association in the first 6 months post-transplant. Variant C allele carriers had significantly higher odds of leukopenia than A/A homozygotes. This study concluded that genetic variation may play a role in the development of leukopenia in patients receiving mycophenolate or antivirals for CMV following heart transplantation and this genetic marker could help identify patients at risk.

Nadziakiewicz P, et al. (2020). Tacrolimus and Mycophenolic Acid Blood Concentration and Cellular Rejection After Heart Transplantation in First Endomyocardial Biopsy. *Transplantation Proceedings*, 52(7), 2094–2097. Retrieved from: <https://doi.org/10.1016/j.transproceed.2020.03.006>

- This study was a retrospective analysis of 39 consecutive adult OHTs to compare kinetics of the immunosuppressants' blood levels in a group of patients with and without graft rejection. Immunosuppressant drug levels were similar between the two groups for mycophenolate and tacrolimus. This study concluded that monitoring of tacrolimus and/or mycophenolate in the early post OHT period does not help identify patients with rejection.

Nguyen LS, et al. (2020). Quadritherapy vs standard tritherapy immunosuppressant regimen after heart transplantation: A propensity score–matched cohort analysis. *American Journal of Transplantation*, 20(10), 2791–2801. Retrieved from: <https://doi.org/10.1111/ajt.15849>

- This study was a 3-year registry cohort of heart transplanted patients, those who received quadritherapy (with low dose everolimus and CNIs plus MMF and CCS) were compared with those who received tritherapy (with standard dose CNIs, MMF, and CCS). 213 patients were included and in the matched cohort, quadritherapy was associated with fewer deaths and BPARs. Renal function and DSAs were similar between groups. This study concluded that Low-dose

combination quadritherapy was associated with fewer deaths and rejections, compared with standard immunosuppression tritherapy.

Bürker BS, et al. (2017). Cognitive function after heart transplantation: Comparing everolimus-based and calcineurin inhibitor-based regimens. *Clin Transplant*, 31:4. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/28185318>

- Given the high prevalence of cognitive impairment in the sample, plus the known negative impact of cognitive impairment on clinical outcome, our results indicate that cognitive assessment should be an integrated part of routine clinical follow-up after HTx. However, everolimus- and CNI-based immunosuppressive regimens did not show differential impacts on cognitive function

Eisen HJ, et al. (2013). Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. *American Journal of Transplantation*, 13:1203–1216. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/23433101>

- Everolimus 1.5 mg and 3 mg daily plus steroids and cyclosporine targeting reduced trough concentration were compared to MMF plus steroids and traditional cyclosporine dosing with and without induction therapy. Patients receiving 3 mg of everolimus daily experienced increased mortality and this regimen was terminated. Everolimus was non-inferior to MMF with respect to the primary composite efficacy endpoint (biopsy-proven acute rejection, acute rejection associated with hemodynamic compromise, graft loss/retransplant, death or loss to follow-up) at 12 and 24 months. Mortality, primarily related to infection, at month 3 was higher when everolimus was combined with rATG induction, but was similar at 24 months.

Page, R. L. et al. (2005). Drug therapy in the heart transplant recipient part iv: drug–drug interactions. *Circulation*, 111:230-239. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15657387>

Lindenfeld J, et al. (2005). Drug therapy in the heart transplant recipient part iii: common medical problems. *Circulation*, 111-117. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15630040>

Lindenfeld J, et al. (2004). Drug therapy in the heart transplant recipient part ii: immunosuppressive drugs. *Circulation*, 110:3858-3865. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15611389>

- These three complete the four-part series reviewing medication management for heart transplant recipients. Maintenance immunosuppression, drug-drug interactions and a variety of common post-transplant disease states including hypertension, hyperlipidemia, coronary allograft vasculopathy, osteoporosis, diabetes and depression are discussed. The series is a bit dated, but provides a nice introduction for students and residents.

### 5.3 Desensitization therapy

Habal, MV (2021). Current desensitization strategies in heart transplantation. *Frontiers in Immunology*, 12:702186. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34504489/>

- This review article discusses tailoring approaches to desensitization in heart transplant recipients through further attention to B cell activation, memory, and plasma cell differentiation to establish methods that durably abrogate the anti-HLA antibody response before and after transplant.

Sriwattanakomen R, et al. (2021). Impact of carfilzomib-based desensitization on heart transplantation of sensitized candidates. *The Journal of Heart and Lung Transplantation*, 40(7):595–603. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33785250/>

- This was a study using carfilzomib for desensitization in heart transplant recipients. They included 9 patients that underwent 20 cycles of carfilzomib based desensitization and found an average cPRA decrease of 24% for IgG and 36% for C1q. Overall from treatment start to finish, mean cPRA fell from 76% to 40% for IgG ( $p=0.01$ ) and 56% to 4% for C1q ( $p=0.017$ ). All patients survived within the follow up time of 35.1 months with only 1 instance of rejection. AKI and thrombocytopenia were the most common side effects both self-resolving.

Saadi TA, et al. (2021). Outcomes of pre- heart transplantation desensitization in a series of highly sensitized patients bridged with left ventricular assist devices. *The Journal of Heart and Lung Transplantation*, 40(10):1107–1111. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34281777/>

- This retrospective study assessed LVAD bridged candidates who received pre-transplant desensitization therapy with IVIG and rituximab followed by bortezomib and PLEX if insufficient response. Of the 10 patients analyzed, median decreased in cPRA was 11% with no significant decrease for 3 patients. All patients had ADEs including coagulopathy, bone marrow suppression, and infection. One patient had rejection and 3 had rising DSAs.

Nguyen LS et al. (2021). Impact of sex in the efficacy of perioperative desensitization procedures in heart transplantation: a retrospective cohort study. *Frontiers in Immunology*, 12:659303. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34305891/>

- This study assessed the effect of desensitization by comparing treated patients to a historical control. The study included 68 patients and found significant protective association between desensitization and events and a deleterious association between cumulative preformed donor-specific DSA and events. There was also a sex difference in the efficacy of desensitization where in men the benefit was significant but not in women. In conclusion, perioperative desensitization was associated with fewer AMR/deaths after transplant with efficacy more pronounced in men.

Plazak ME, et al. (2021). Clinical outcomes of perioperative desensitization in heart transplant recipients. *Transplantation Direct*, 7(2), e658. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33521247/>

- Single center, retrospective study of adults who received heart transplant and perioperative desensitization if virtual crossmatch or flow-cytometry crossmatch was positive. Patients received PLEX, IVIG, and rATG compared with historical controls with standard immunosuppression or induction. Of the 104 patients included, 10 received desensitization and there were no differences in the primary endpoint of survival at 12 months. Rates of acute rejection were lower with induction and desensitization than no induction. There were no differences in CAV.

Alishetti S, et al. (2020). Desensitizing highly sensitized heart transplant candidates with the combination of belatacept and proteasome inhibition. *American Journal of Transplantation*, 20(12), 3620–3630. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32506824/>

- This study treated 4 highly sensitized heart transplant candidates with belatacept and PI therapy and found a significant reduction in both class I and II HLA antibodies and an increased likelihood of identifying an acceptable donor. This study found synergism between PI based desensitization and belatacept facilitating transplantation with a negative CDC crossmatch against C1q binding antibodies.

Timofeeva OA, et al. (2020). Serum dilutions as a predictive biomarker for peri-operative desensitization: An exploratory approach to transplanting sensitized heart candidates. *Transplant Immunology*, 60: 101274. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32142756/>

- This study investigated sera dilutions as a potential to guide therapeutic plasma exchange regimens for effective peri-operative desensitization and early AMR treatment in heart transplant

patients. The data revealed that 1:16 dilutions of EDTA-treated sera and 1.5 volume TPE reduced anti-HLA class I/class II antibody levels and allowed the investigators to predict which antibodies would respond to peri-operative plasma exchange. Using their results, they transplanted three highly sensitized cardiac recipients with peri-operative desensitization based on a virtual crossmatch performed on 1:16 diluted serum, and have used sera dilutions to guide DSA treatment post-transplant.

Kransdorf EP, et al. (2017). Calculated panel-reactive antibody predicts outcomes on the heart transplant waiting list. *J Heart Lung Transplant*. 2017 Feb 17. pii: S1053-2498(17)31624-8. Retrieved from: [www.ncbi.nlm.nih.gov/pubmed/28318744](http://www.ncbi.nlm.nih.gov/pubmed/28318744)

- Sensitized heart transplant candidates are at high risk of adverse outcomes on the heart transplant waiting list. Clinicians should strive to minimize the CPRA by maximizing specificity in the selection of HLA antigens to exclude. The optimal clinical approach for candidates with high CPRA requires further study.

Eckman PM, et al. (2010). Immunosuppression in the sensitized heart transplant recipient. *Current Opinion in Organ Transplantation*, 15, 650–656. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20689437>

- This article reviews contemporary approaches to desensitization prior to and immunosuppression following heart transplant.

Patel J, et al. (2011). Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. *J Heart Lung Transplant*, 30, 1320 – 6. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21968130>

- The first clinical experience using a plasma-cell-depleting strategy with bortezomib to reduce anti-HLA antibodies in the heart transplant population.

Kobashigawa JA, et al. (2011). The long-term outcome of treated sensitized patients who undergo heart transplantation. *Clin Transplant*, 25, E61–E67. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20973825>

- This study was done to determine whether reduction in circulating antibodies pre-transplant with plasmapheresis, intravenous gamma globulin and rituximab improves post-transplant outcomes.

Morrow WR, et al. (2012). Rapid reduction in donor-specific anti-human leukocyte antigen antibodies and reversal of antibody-mediated rejection with bortezomib in pediatric heart transplant patients. *Transplantation*, 93, 319–324. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22179403>

- This article documents the first use of bortezomib for cardiac transplant recipients in four pediatric heart recipients with biopsy-proven AMR, hemodynamic compromise, positive crossmatch, and high titer class I DSA.

Zeevi A, et al. (2012). HLA antibody profiling in thoracic transplantation undergoing desensitization therapy. *Curr Opin Organ Transplant*, 17, 416–422. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22790076>

- This article reviews HLA antibody profiling pre-transplant and the effect of desensitization protocols on post-transplant outcomes.

Urban M, et al. (2012). Alloimmunosenesitization in left ventricular assist device recipients and impact on posttransplantation outcome. *ASAIO Journal*, 58, 554–561. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23069898>



- This article presents the current state of knowledge of possible immunologic mechanisms involved in alloimmunization of LVAD recipients, outlines new methods of antibody detection, compares various desensitization strategies, and presents an overview of clinical data assessing the impact of sensitization on post-transplantation outcome.

Chang D, et al. (2012). The use of the calculated panel reactive antibody and virtual crossmatch in heart transplantation. *Curr Opin Organ Transplant*, 17, 423–426. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22790077>

- This article reviews the use of calculated panel reactive antibody and virtual crossmatch in heart transplant as well as current desensitization strategies.

Picascia A, et al. (2012). Current concepts in histocompatibility during heart transplant. *Experimental and Clinical Transplantation*, 3, 209-218. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22631055>

- This article reviews strategies for detection of antibodies and current strategies for desensitization pre-transplant.

Kaufman, BD et al. (2011). Immunologic considerations in heart transplantation for congenital heart disease. *Current Cardiology Reviews*, 7, 67-71. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22548029>

- This article reviews the causes of anti-HLA antibody production (allosensitization), preventive strategies for allosensitization before transplantation, treatment strategies for allosensitization before transplantation, consequences of HLA allosensitization after transplantation and treatment of HLA allosensitization and antibody-mediated rejection after transplantation.

Chih S, et al. (2016). Desensitization strategies in adult heart transplantation-Will persistence pay off? *J Heart Lung Transplant*, 35(8):962-72. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/27216504/>

- Review article of desensitization strategies in adult heart transplantation. No approach has demonstrated significant and sustainable reductions in HLA antibody pre-transplant, and the ideal desensitization strategy remains elusive. In addition, clinical tools to evaluate the humoral response and efficacy of therapy are limited, focusing almost exclusively on HLA antibody detection. Importantly, desensitization is associated with significant costs and potential risks, and overall long-term outcomes and cost-effectiveness have not been sufficiently evaluated.

Geft D, et al. (2017). Current concepts for sensitized patients before transplantation. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28306593>

- The development of more accurate methods of detecting sensitization and defining the ideal desensitization strategies that can be more universally adopted and tested in clinical trials will serve to enlighten us and help many more highly sensitized patients not only make it to transplant, but also thrive posttransplant as well.

Nakamura et al. (2018). Successful heart transplantation after desensitization in a patient with extremely high panel-reactive antibody levels and pretransplant donor-specific antibody: a case report. *Transplant Proc*, 50 (10): 4067-4070. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/30577317>.

- Case report describing the successful desensitization of a heart transplant recipient with severely elevated panel reactive antibody (PRA) and pre-transplant DSA positivity.

Shah et al. (2019). Desensitization in heart transplant recipients: who, when, and how. *Clin Transplant*, 33(8). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/31206862>.

- Review discussing status of antibody detection and identification, strength, and potential pathogenicity. Therapies such as mechanical removal of antibodies, IVIG, and novel immunosuppressive agents will be discussed.

Edwards et al. (2019). Impact and predictors of positive response to desensitization in pediatric heart transplant candidates. *J Heart Lung Transplant*, 38 (11):1206-1213. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/31672220>.

- Patients were categorized as sensitized receiving desensitization, sensitized and not receiving desensitization, or non-sensitized. Desensitization response was found in 8 patients upon repeat PRA testing after administration of IVIG. Factors such as ventricular assist device (VAD) and homograft combination were found to cause higher sensitization than either of the two alone. Patients undergoing sensitization therapy were associated with an increased likelihood of remaining listed longer and a longer time on the waitlist without impact on the rate of transplantation, mortality, or post-transplantation outcomes.

## 5.4 Rejection Management

### 5.4.1 Rejection - General

Afzal A, et al. (2022). Observed elevated donor-derived cell free DNA in orthotopic heart transplant recipients without clinical evidence of rejection. *Clin Transplant*, 36(3):314549. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/34863042/>

- Retrospective cohort study evaluated possible confounders warranting the need for more intelligent use of this non-invasive surveillance technique. Recipients who experienced dd-cfDNA  $\geq 0.20\%$  in the absence of clinical rejection were analyzed and revealed four distinct groups characterized by (a) subclinical rejection with 50% CMV (n = 16), (b) non-CMV infections and the longest time to first elevated dd-cfDNA (187 days) (n = 8), (c) right ventricular dysfunction (n = 6), and (d) women who showed the youngest median age (45 years) and highest median dd-cfDNA (0.50%) (n = 5).

Kewcharoen J, et al. (2022). Initiation of noninvasive surveillance for allograft rejection in heart transplant patients > 1 year after transplant. *Clin Transplant*, 36(3):e14548. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/34843112/>

- This retrospective cohort study described their use of gene expression profiling (GEP) and dd-cfDNA in heart transplant recipients > 1-year post-transplantation. Among nine EMBs, one sample showed acute cellular rejection grade 2R due to elevations of both GEP and dd-cfDNA. This study showed use of both GEP and dd-cfDNA led to an increased number of EMB in patients > 1-year post-transplantation.

Knuttgen F, et al. (2022). Graft-derived cell-free DNA as a noninvasive biomarker of cardiac allograft rejection: a cohort study on clinical validity and confounding factors. *Transplantation*, 106(3):615-622.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33653997/>

- Prospective cohort study included 87 patients and 770 serial dd-cfDNA samples drawn at predefined time-points. The study found dd-cfDNA plasma values were significantly associated with cardiac rejection. Confounding factors identified included pericardial effusions and improper sampling (e.g. shortly after biopsy) which should be considered when dd-cfDNA is used for rejection diagnoses.

Qian X, et al. (2022). Noninvasive biomarkers in heart transplant: 2020–2021 year in review. *Current Opinion in Organ Transplantation*. 2022;27(1):7-14. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34939959/>

- This article reviewed recent advances in the field of noninvasive biomarkers to detect allograft rejection after heart transplant. Noninvasive biomarkers discussed include donor-derived cell-free DNA (dd-cfDNA), MicroRNAs, high-sensitive cardiac troponin (hs-cTnI), N-terminal pro-brain natriuretic peptide (NTproBNP), donor-specific antibodies (DSAs), and circulating extracellular vesicles (EVs)

Slomovich S, et al. (2021). Extracorporeal photopheresis and its role in heart transplant rejection: prophylaxis and treatment. *Clinical Transplantation*, 35(7):e14333. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33914369/>

- This review discusses extracorporeal photopheresis and summarizes the current data on its use for prophylaxis and therapy in heart transplant rejection.

Boutolleau D, et al. (2021). Association between cytomegalovirus infection and allograft rejection in a large contemporary cohort of heart transplant recipients. *Transplant Infectious Disease*, 23(4):e13569. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33452851/>

- This was a single center cohort study that utilized a database of heart transplant patients to determine association between CMV and allograft rejection. Out of the 384 patients included, there was no association between CMV and rejection

Peyster EG, et al. (2020). In situ immune profiling of heart transplant biopsies improves diagnostic accuracy and rejection risk stratification. *JACC: Basic to Translational Science*, 5(4):328–340. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32368693/>

- This was a retrospective cohort of clinical endomyocardial tissue samples that found that in situ immune modulators (such as ligand 1+, 68+ cells, forkhead box P3+ regulate the severity of cardiac allograft rejection.

Itoda Y, et al. (2020). Ventricular assist device bridging with gender-mismatch increases rejection and decreases survival following a heart transplant. *European Journal of Cardio-Thoracic Surgery*, 59(1):217–225. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33057607/>

- This study obtained data from the UNOS database and divided patients into VAD recipients who received a heart from a gender matched donor (VAD-M), VAD recipients who received a heart from a gender mismatched donor (VAD-MM), noVAD recipients who received a heart from a gender matched donor (noVAD-M), and noVAD recipients that received a heart from a gender mismatched donor (noVAD-MM). They found in an adjusted survival analysis that the VAD-MM group showed significantly worse survival than the VAD-M group with no difference between the noVAD-M and noVAD-MM groups.

Adamson MB, et al. (2020). HLA-G +3196 polymorphism as a risk factor for cell mediated rejection following heart transplant. *Human Immunology*, 81(4):134–140. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31928922/>

- HLA-G expression is associated with rejection and this study objective was to evaluate polymorphisms and cell mediated rejection (CMR). 123 recipients were randomized to identify polymorphisms, they found the CG genotype polymorphism was associated with reduced CMR risk and the +3196 G allele was a risk factor for CMR.

Osorio-Jaramillo E, et al. (2020). Molecular-level HLA mismatch is associated with rejection and worsened graft survival in heart transplant recipients – a retrospective study. *Transplant International*, 33(9):1078–1088. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32441827/>

- This was a retrospective study to look at HLA mismatching with post-transplant graft survival, rejection, and CAV. They analyzed 1167 patients and found that patients with a higher HLA-DR AMM load had inferior 1 year graft survival. They also found that HLA-AB increasing load had a higher risk of rejection.

Poglajen G, et al. (2017). Low serum testosterone is associated with graft function early after heart transplantation. *Clin Transplant*. [Epub ahead of print]. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/28314079>

- Low serum testosterone levels appear to be associated with impaired graft function and an increased incidence of low-grade rejection episodes early after heart transplantation.

Savignano C, et al. (2017). Extracorporeal photochemotherapy in heart transplant rejection: a single-center experience. *Transfus Apher Sci*, 56 (4): 520-524. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/28774825>.

- This is a retrospective analysis of heart transplant recipients receiving maintenance immunosuppression and extracorporeal photochemotherapy (ECP) for the treatment of rejection. Patients received ECP for recurrent rejection, persistent rejection, and mixed rejection with hemodynamic compromise. Patients receiving ECP had a low response rate (37.5%) when added to maintenance immunotherapy likely due to patient selection. Larger clinical trials are needed to determine the utility of ECP in heart rejection treatment or prophylaxis.

Kfoury AG, et al. (2016). Mixed cellular and antibody-mediated rejection in heart transplantation: In-depth pathologic and clinical observations. *J Heart Lung Transplant*, 35(3):335-41. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Mixed+cellular+and+antibody-mediated+rejection+in+heart+transplantation%3A+In-depth+pathologic+and+clinical+observations>.

- Mixed rejection is not common, usually occurs early after transplant, and is associated with worse outcomes. Mixed rejection reflects a complex interplay between cellular and humoral processes, which varies with rejection severity.

Patel J, et al. (2015). Extracorporeal photopheresis in heart transplant rejection. *Transfus Apher Sci*, 52(2):167-70. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25748232>.

- Extracorporeal photopheresis (ECP) appears particularly useful in the management of select heart transplant recipients at risk of rejection, with recurrent rejection, or rejection associated with hemodynamic compromise. This summarizes the current clinical experience of ECP in heart transplantation.

Imamura T, et al. (2013). Successful treatment of hemodynamic compromise caused by antibody-mediated and cellular rejection in a recipient 12 years after heart transplantation. *Int Heart J*, 54, 328-331. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24097224>

- This is a case report of successful treatment of rejection with repeated plasma exchange accompanied by a single administration of rituximab. The case of rejection was refractory to repeated steroid pulse treatment, intravenous immunoglobulin administration and intensifying immunosuppression.

Patel JK, et al. (2011). Cardiac allograft rejection. *The Surgeon*, 9, 160-167. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21550522>

- This article is a review of the current status of the diagnosis of cardiac allograft rejection as determined by the traditional endomyocardial biopsy, the more recent advances in the non-invasive evaluation of rejection, detection of circulating antibodies and the treatment of rejection.

Patel JK, et al. (2004). Immunosuppression, diagnosis, and treatment of cardiac allograft rejection. *Semin Thorac Cardiovasc Surg*, 16:378-385. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15635544>

- This is a review article that addresses immunosuppression post-transplant as well as the diagnosis and treatment of cardiac allograft rejection.

#### 5.4.2 **Acute Cellular Mediated Rejection**

Halloran PF, et al. (2022). Many heart transplant biopsies currently diagnosed as no rejection have mild molecular antibody-mediated rejection-related changes. *J Heart Lung Transplant*, 41(3):334-344. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34548198/>

- Study extended the Molecular Microscope (MMDx) methodology to define a new “Minor” category characterized by low-level inflammation in non-rejecting biopsies and found many heart transplants currently diagnosed as no-rejection by histologic or molecular assessment have minor increases in ABMR-related and IFNG-inducible transcripts, associated with DSA positivity and mild histologic inflammation.

Nelson LM, et al. (2020). Mild acute cellular rejection and development of cardiac allograft vasculopathy assessed by intravascular ultrasound and coronary angiography in heart transplant recipients—a SCHEDULE trial substudy. *Transplant International*, 33(5):517–528. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31958178/>

- This study evaluated the associated between ACR and development of CAV after heart transplant. It is a substudy of SCHEDULE which included 115 patient who received everolimus w/ CNI elimination or CNI based immunosuppression. They found that ACR was recorded in 67% of patients and median maximal intimal thickness was not different between ACR and no ACR groups. The incidence of CAV was no difference between groups.

Mateo R, et al. (2015). Relationship between hyperglycemia and heart transplant rejection. *Transplant Proc*, 47(9):2727-31. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26680082>

- Grade  $\leq 1R$  rejection on biopsy was observed in 116 patients and grade  $\geq 2R$  rejection (grade requiring increased anti-rejection treatment) in 41 patients. Although no significant differences in the preoperative fasting or inpatient mean glucose levels were found, the mean glucose levels from discharge to 1 year trended higher in those with grade  $\geq 2R$  compared to grade  $\leq 1R$  ( $128.8 \pm 40.9$  versus  $142.2 \pm 46.6$  mg/dL,  $P = .084$ ).

Ankersmit HJ, et al. (2003). Rapamycin as rescue therapy in a patient supported by biventricular assist device to heart transplantation with consecutive ongoing rejection. *American Journal of Transplantation*, 3, 231—234. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/12603219>

- This is a case report of cardiac allograft rejection despite treatment with anti-thymocyte globulin (ATG), FK506, a mycophenolate switch and courses of multiple apheresis that was successfully treated with Rapamycin.

Lehrer MS, et al. (2001). Successful reversal of severe refractory cardiac allograft rejection by photopheresis. *J Heart Lung Transplant*, 20:1233–1236. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11704486>

- This is a case report of 4 patients with refractory International Society of Heart and Lung Transplantation Grades IIIA to IV cardiac allograft rejection treated successfully with extracorporeal photopheresis.

### 5.4.3 Acute Antibody Mediated Rejection

Yopes M, et al. (2022). Chronic intermittent intravenous immunoglobulin in heart transplant recipients with elevated donor-specific antibody levels. *Clinical Transplantation*. 2022;36(2). Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34705286/>

- Retrospective cohort study evaluated 19 patients receiving chronic intermittent IVIG for elevated DSA that examined changes in DSA, MFI and allograft function (LVEF, CI)

Yerly P, et al. (2022). Complement blockade with eculizumab to treat acute symptomatic humoral rejection after heart transplantation. *Xenotransplantation*, 29(1):e12726. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35001433/>

- Case report of a heart transplant recipient presenting with late acute AMR. The patient fully recovered allograft function and completely cleared DSA following plasmapheresis-free upfront eculizumab administration along with thymoglobulin, IVIG, and rituximab.

Erdogan I, et al. (2018). Rituximab therapy for rejection in pediatric heart transplant. *Exp Clin Transplant*, 16 (2): 199-203. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27210774>.

- Case series of seven pediatric heart transplant patients were treated with plasma exchange (PLEX) and rituximab for antibody-mediated rejection post-heart transplantation. Overall, 5 patients experienced refractory persistent rejection required repeat doses of rituximab. A total of 4 patients died after diagnosis of AMR but not related to complications or adverse effects from rituximab.

Clerkin KJ, et al. (2017). Donor-specific anti-HLA antibodies with antibody-mediated rejection and long-term outcomes following heart transplantation. *J Heart Lung Transplant*. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27916323>

- DSA were inadequate to diagnose pAMR. Class II DSA provided prognostic information regarding future pAMR, graft dysfunction with pAMR, and graft loss.

Loupy A, et al. (2017). Gene expression profiling for the identification and classification of antibody-mediated heart rejection. *Circulation*, 135 (10): 917-935. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28148598>.

- This prospective study aimed to assess endomyocardial biopsies to detect antibody-mediated rejection (AMR) across 4 transplant centers. Patients experiencing AMR showed a distinct pattern of injury characterized with inflammatory markers including monocytes/macrophages and natural killer cells directly correlating to the degree of injury and disease activity. This study demonstrates the potential utility of tissue based analysis for patients' experiencing AMR.

Manfredini V, et al. (2017). Antibody-mediated rejection in heart transplantation: new developments and old uncertainties. *Curr Opin Organ Transplant*. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28301387>

- Despite improvements in the diagnostic process, therapeutic strategies made little progress in addition to the consolidation of practices supported by limited evidence. Novel complement inhibitors appear promising in changing this scenario. Nevertheless, collaborative multicenter studies are needed to develop standardized approaches tailored to the highly variable clinical and laboratory features of AMR.

Tran A, et al. (2016). Donor-specific HLA alloantibodies: Impact on cardiac allograft vasculopathy, rejection, and survival after pediatric heart transplantation. *J Heart Lung Transplant*, 5(1):87-91. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26422083/>

- Of the 105 patients, 45 (43%) developed de novo DSA. DSA-positive patients had significantly higher rates of coronary artery vasculopathy (CAV) compared with DSA-negative patients (36% vs 13%). The 5-year graft survival rate was 72.4% for DSA-negative patients and 21% for DSA-positive patients (< 0.001). De novo DSA has a strong negative impact on CAV, rejection, and graft survival in pediatric recipients of heart transplants.

Coutance G, et al. (2015). Late antibody-mediated rejection after heart transplantation: Mortality, graft function, and fulminant cardiac allograft vasculopathy. *J Heart Lung Transplant*, 34(8):1050-7. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/25956740/>

- Prognosis after late AMR is poor despite aggressive immunosuppressive therapies. Fulminant CAV is a common condition in these patients. Microvascular inflammation is frequent in endomyocardial biopsy specimens before manifestation of symptomatic AMR.

Gazdic T, et al. (2015). Bortezomib-containing regimen for primary treatment of early antibody-mediated cardiac allograft rejection: a case report. *Prog Transplant*, 25(2):147-52. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26107275/>

- Primary treatment with a bortezomib-containing regimen appears to be a new therapeutic option for severe antibody-mediated rejection in heart transplant recipients.

Kaczorowski DJ, et al. (2013). Profound hyperacute cardiac allograft rejection rescue with biventricular mechanical circulatory support and plasmapheresis, intravenous immunoglobulin, and rituximab therapy. *Journal of Cardiothoracic Surgery*, 8:48. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23497431>

- This is a case report of hyperacute rejection managed with ventricular assist devices (VADs) for biventricular support during treatment with rituximab, intravenous immunoglobulin (IVIG), and plasmapheresis.

Chih S, et al. (2013). A survey of current practice for antibody rejection in heart transplantation. *American Journal of Transplantation*, 13:1069–1074. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23414257>

- This article reviewed and analyzed online survey data from 184 ISHLT members from medium to large volume adult transplant centers in North America and Europe to determine their practices regarding criteria for initiating treatment for rejection and the treatment of antibody mediated rejection.

Aggarwal A, et al. (2012). Low-dose rituximab therapy for antibody-mediated rejection in a highly sensitized heart-transplant recipient. *Tex Heart Inst J*, 39(6):901-5. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23304051>

- This is a case report regarding the role of low-dose rituximab as therapy for antibody-mediated rejection in heart-transplant patients.

Nair N, et al. (2011). Current and future challenges in therapy for antibody-mediated rejection. *J Heart Lung Transplant*, 30, 612–7. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21474341>

- This article discusses the challenges in treating antibody mediated rejection and provides a critical analysis of current and possible future therapies.

Jhang J, et al. (2007). Therapeutic plasma exchange performed in parallel with extra corporeal membrane oxygenation for antibody mediated rejection after heart transplantation. *Journal of Clinical Apheresis*, 22, 333–338. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18080271>

- This is a case report demonstrating the use of therapeutic plasmapheresis in parallel with extracorporeal membrane oxygenation to alleviate antibody mediated rejection.

Kaczmarek I, et al. (2007). Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-cd20 monoclonal antibody treatment: Case report and literature review. *J Heart Lung Transplant*, 26, 511–5. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17449422>

- This is a case report of a patient with antibody mediated rejection who was successfully treated with 3 cycles of immunoadsorption and a single-dose administration of rituximab.

Garrett Jr. EH, et al. (2005). Treatment of vascular rejection with rituximab in cardiac transplantation. *J Heart Lung Transplant*, 24, 1337–42. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16143254>

- This is a case report of 8 patients with antibody mediated rejection successfully treated with rituximab at a dose of 375 mg/m<sup>2</sup> per week for 4 weeks.

Baran, DA et al. (2004). Refractory humoral cardiac allograft rejection successfully treated with a single dose of rituximab. *Transplantation Proceedings*, 36, 3164–3166. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15686719>

- This is a case report of refractory humoral cardiac rejection successfully treated with a single dose of rituximab 375 mg/m<sup>2</sup>.

Aranda JM, et al. (2002). Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report. *Transplantation*, 73:6, 907–910. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11923690>

- This is a case report of humoral rejection resistant to steroids, cyclophosphamide, and plasmapheresis successfully treated with rituximab.

Grauhan O, et al. (2001). Plasmapheresis and cyclophosphamide in the treatment of humoral rejection after heart transplantation. *J Heart Lung Transplant*, 20:316–321. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11257558>

- This is a retrospective study evaluating the use of corticosteroids and cytolytic antibodies vs. corticosteroids, cytolytic antibodies, and plasmapheresis to treat humoral rejection post heart transplant.

#### **5.4.4 Rejection Surveillance**

Agbor-Enoh S, et al. (2021). Cell-Free dna to detect heart allograft acute rejection. *Circulation*, 143(12):1184–1197. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33435695/>

- This was a multicenter, prospective cohort study that recruited heart transplant patients and collected plasma samples with endomyocardial biopsy (EMBX) for %ddcfDNA measurement. They included 171 patients and found that median %ddcfDNA levels decayed after surgery and



then increased in relation to diagnosis of ACR/AMR. %ddcfDNA had a negative predictive value for rejection of 99% and would have safely eliminated 81% of EMBx. This study found that %ddcfDNA monitoring could have earlier detection than EMBx based monitoring for ACR/AMR.

Castellani C, et al. (2020). Circulating extracellular vesicles as non-invasive biomarker of rejection in heart transplant. *The Journal of Heart and Lung Transplantation*, 39(10):1136–1148. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/32665078/>

- This study aimed to investigate differences in plasma derived extracellular vesicles (EVs) surface protein profiles as a biomarker to use in combination with endomyocardial biopsies (EMBx) for diagnosis of rejection. This study found that the concentration of EVs was significantly increased and diameter decreased in patients undergoing rejection. The trend was highly significant for both AMR and ACR. This study concluded that circulating EVs could be a promising new tool to characterize cardiac allograft rejection and be complementary to EMB monitoring.

Zhang X, et al. (2020). Association of vimentin antibody and other non-HLA antibodies with treated antibody mediated rejection in heart transplant recipients. *Human Immunology*, 81(12):671–674.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33041085/>

- This study utilized a selected cohort of patients without HLA DSAs but diagnosed with AMR and found the presence of vimentin antibody that was associated with AMR. Therefore they suggest that heart transplant patients should be examined for non-HLA antibodies as well.

Agbor-Enoh S, et al. (2017). Applying rigor and reproducibility standards to assay donor-derived cell-free dna as a non-invasive method for detection of acute rejection and graft injury after heart transplantation. *J Heart Lung Transplant*, 36 (9): 1004-1012. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/28624139>.

- Quantitative genomic techniques such as donor-derived cell-free DNA (%ddcfDNA) assays were found to be precise and reproducible across multiple laboratories and able to detect both cellular and antibody mediated rejection. Larger studies utilizing this technique are needed to determine the exact clinical utility of %ddcfDNA as an acute marker for episodes of cellular or acute antibody mediated rejection.

## 5.5 Graft Failure/Primary Graft Dysfunction (PGD)

Smith NF, et al. (2022). Primary graft dysfunction in heart transplant recipients-risk factors and longitudinal outcomes. *ASAIO J*, 68(3):394-401. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/34593684/>

- Single-center, retrospective cohort study investigated primary graft dysfunction (PGD) by applying the ISHLT consensus definition to identify risk factors and long-term outcomes. The incidence of PGD was 16.5% (n = 74). The study found development of PGD is associated with higher 30 day-, 1 year-, and 5 year-mortality (p < 0.0001). Risk factors associated with PGD include prolonged ischemic time and multiple perioperative transfusions.

Jernryd V, et al. (2022). Myocardial injury biomarkers at point of care for early identification of primary graft dysfunction after heart transplantation. *Clinical Transplantation*. 2022;36(2). Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/34738670/>

- Prospective observational study found patients with high CK-MB ( $\geq 11$  ng/ml) had an increased risk for severe graft dysfunction (p = 0.037). Similar but non-significant trends were observed for cTnl.

Chinnadurai T, et al. (2022). The interaction of amiodarone and continuous-flow left ventricular assist device use in risk of severe primary graft dysfunction following heart transplantation. *Transplant Direct*, 8(2):e1281. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35047663/>

- Single-center retrospective study that evaluated risk factors for severe PGD. Severe PGD was independently associated with amiodarone use and CF-LVAD use, and a higher prevalence was found if both risk factors were present (CF-LVAD-/amiodarone- 1.5%, CF-LVAD-/amiodarone+ 4.5%, CF-LVAD+/amiodarone- 7.1%, CF-LVAD+/amiodarone+ 21.8%;  $p < 0.01$ ).

Truby LK, et al. (2021) Proteomic profiling identifies CLEC4C expression as a novel biomarker of primary graft dysfunction after heart transplantation. *J Heart Lung Transplant*. 40(12):1589-1598. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8670564/>

- Single center study from 2016 to 2020 at Duke University Medical Center to identify whether pre-transplant levels of circulating proteins on immune activation and inflammation are associated with incident of primary graft dysfunction (PGD)
- 219 adult heart transplant were randomly divided in derivation ( $n=131$ ) and validation ( $n=88$ ) sets. Nine proteins were associated with PGD in univariate models in the derivation set. Only CLEC4C, a protein marker of plasmacytoid dendritic cells (pDCs), remained associated with PGD in the validation set. The study concluded that pre-transplantation circulating levels of CLEC4C may identify heart transplant patients at risk for PGD

Noly PE, et al. (2021). Use of extracorporeal membrane oxygenation for heart graft dysfunction in adults: Incidence, risk factors and outcomes in a multicentric study. *Can J Surg*, 64(6):E567-E577. Retrieved from: <https://doi.org/10.1503/cjs.021319>

- Multicenter retrospective cohort study in France and Canada from January 2003 to December 2013. Of 135 patients who had graft dysfunction after OHT, 66 received VA-ECMO, and 69 received medical treatment alone. Of those who received VA-ECMO, 40 received early VA-ECMO in the first 24-hours after OHT, and 26 received delayed VA-ECMO after 24-hours after OHT.
- In hospital mortality was higher in patients requiring VA-ECMO (57%) than in patients managed with medication alone (14%) ( $p = 0.001$ ). Overall survival was lower in the VA-ECMO group at both 1 and 5 years (42% vs. 83%; 40% vs. 78%). Survival was very poor in the delayed VA-ECMO group (12 vs. 60% at 1 year,  $p < 0.001$ ). The incidence of graft dysfunction increased over the course of the study period of ten years from 23% to 41%, and rates of VA-ECMO increased over the study period. However, hospital mortality rate decreased over the study period in all patients.

Jernryd V, et al. (2021). Myocardial injury biomarkers at point of care for early identification of primary graft dysfunction after heart transplantation. *Clin Transplant*, e14526. Retrieved from: <https://doi.org/10.1111/ctr.14526>

- Single center prospective cohort study performed in Lund, Sweden from March 2015 to October 2018. The aim of the study was to assess whether cardiac biomarkers in donor hearts after being flushed with blood cardioplegia from the recipient to determine if severe primary graft dysfunction (PGD) could be assessed early in the transplant process.
- Of the 63 patients enrolled in the study, eight patients (13%) were diagnosed with severe PGD that the center treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO). Those with severe PGD had an average creatine kinase-muscle brain (CK-MB) of 10.6 ng/mL compared to an average CK-MB of 6.3 ng/mL in those who did not develop PGD ( $p = 0.55$ ). Only 14 out of the 63 patients had high CK-MB of 11 ng/mL or greater, and 4 of the 14 patients

developed severe graft dysfunction ( $p = 0.065$ ). When adjusted for multiple variables, donor hearts with a CK-MB of 11 ng/mL or greater had an adjusted odds ratio of 7.4 ( $p = 0.037$ ).

Nagy A, et al. (2021). Endocrine management and hormone replacement therapy in cardiac donor management: A retrospective observational study. *Transplant Proc*, S0041-1345(21):00696-5. Retrieved from: <https://doi.org/10.1016/j.transproceed.2021.08.048>

- Single center retrospective observational study in Hungary from January 2012 to September 2018. 297 cardiac donors after brain death were included in the final analysis. The donors had a median age of 41 years and were largely male (73.7%). The recipients had a median age of 54 years and were also largely males (74.1%).
- 56 patients who were recipients of heart transplants developed primary graft dysfunction (PGD) (18.9%), and 43 (76.8%) of the 56 required mechanical circulatory support (MCS). 63 donors (21.2%) donors developed central diabetes insipidus (CDI), which is a sign of pituitary and endocrine dysfunction after brain death. 43 of the donors with CDI (68.3%) were treated with desmopressin or vasopressin. Neither CDI nor the use of desmopressin/vasopressin showed no association with PGD.
- Thyroxine replacement in donors was associated with a significant decrease in PGD development in recipients ( $p = 0.015$ ). It was also associated with a decrease in 30-day mortality ( $p = 0.028$ ). The use of thyroxine and methylprednisolone together showed less PGD than thyroxine use alone ( $p = 0.001$  vs.  $p = 0.006$ ), but there was no significant change in survival when comparing the combination of medications vs. thyroxine alone.

Mehdiani A, et al. (2021). Extracorporeal membrane oxygenation after heart transplantation: Impact of type of cannulation. *Thorac Cardiovasc Surg*, 69(3):263-270. Retrieved from: <https://doi.org/10.1055/s-0039-3400472>

- Single center retrospective cohort study performed in Germany from October 2010 to October 2017 to compare peripheral and central annulation for extracorporeal life support (ECLS) in patients requiring ECMO due to PGD
- Weaning of ECMO was successful in 7 of 10 patients in the central ECMO group (cECMO) and in 7 of 15 patients in the peripheral ECMO group (pECMO) ( $p = 0.414$ ). There were no significant differences in adverse events or in 30-day mortality between the two groups. There was no difference in 1-year mortality in the 18 of 25 patients who were able to follow-up.

Lim HS, et al. (2021). Cardiac power output index and severe primary graft dysfunction after heart transplantation. *J Cardiothorac Vasc Anesth*, 35(2):398-403. Retrieved from: <https://doi.org/10.1053/j.jvca.2020.07.020>

- Single center retrospective cohort study performed in the United Kingdom from January 2014 to December 2019 to determine if cardiac power output index (CPOi) can help predict severe primary graft dysfunction after heart transplant.
- 22 out of 140 study patients developed severe PGD. These patients has a significantly lower CPOi at time of transplant and at 6 hours after transplant. The study indicated that low CPOi at time of transplant is associated with severe PGD, and further testing of CPOi increases the likelihood that the diagnosis of PGD is accurate.

Loforte A, et al. (2021). Mechanically supported early graft failure after heart transplantation. *Transplant Proc*, 53(1):311-317. Retrieved from: <https://doi.org/10.1016/j.transproceed.2020.07.005>

- Single center retrospective cohort study performed in Italy from January 2000 to December 2019 to determine the risk factors for mechanical circulatory supported severe early graft failure (EGF) and to determine the impact of EGF on early and late outcomes after heart transplant.

- The majority of ECMO use was due to PGD (68.5%), and the remainder of cases needing ECMO were due to secondary graft failure (SGF). The EGF group had an early mortality rate of 53.1% compared to 5.5% in the non-EGF group ( $p < 0.001$ ). Independent factors that were associated with EGF were pre-operative transpulmonary gradient  $> 12$  mmHg, pre-operative inotropic score  $> 10$ , and pre-operative ECMO support. A donor score of 17 or greater was also associated with EGF occurrence. Long-term survival was significantly better in those without EGF (94% at 1 year, 85% at 5 years) compared to those with EGF (36% at 1 year, 28% at 5 years) ( $p < 0.001$ ).

Kim HR, et al. (2020). The effect of supplemental cardioplegia infusion before anastomosis in patients undergoing heart transplantation with long ischemic times. *Korean J Thorac Cardiovasc Surg*, 53(6):375-380. Retrieved from: <https://doi.org/10.5090/kjtcs.19.091>

- Single center prospective cohort study performed in South Korea from February 2010 to December 2014. This study aimed to determine the outcomes of giving supplemental cardioplegia in patients with long ischemic times.
- There were no significant differences in PGD or mortality between the cardioplegia group (CPS+) and the non-cardioplegia group (CPS-). There were no significant differences in overall survival at 5-years ( $p = 0.7$ ).

Nakamura Y, et al. (2020). Intraoperative hemoglobin level and primary graft dysfunction in adult heart transplantation. *Gen Thorac Cardiovasc Surg*, 68(11):1260-1269. Retrieved from: <https://doi.org/10.1007/s11748-020-01360-z>

- Single center retrospective cohort study performed in Japan from 2007 to 2016 to determine if serum hemoglobin level at time of transplant impacts the risk of developing PGD after transplant.
- Mean serum hemoglobin level at time of reperfusion was lower in the PGD group than in the non-PGD group ( $p = 0.009$ ). The transfusion volume was higher in the PGD group as well ( $p = 0.003$ ).
- In-hospital mortality was higher in the group that developed PGD compared to the group that did not develop PGD (25.0 % compared to 1.8%,  $p < 0.05$ ). Post-op intubation time and length of stay in the ICU were also significantly longer in the PGD group compared to the non-PGD group (106 hours vs. 37 hours intubated; 24 days vs. 5 days in the ICU;  $p < 0.0001$ ). 1-year survival was lower in the PGD group compared to the non-PGD group (75% vs. 95.9%,  $p = 0.004$ ).

Urban M, et al. (2020). Impact of temporary mechanical circulatory support for early graft failure on post-heart transplantation outcomes. *Clin Transplant*, 34(11):e14060. Retrieved from: <https://doi.org/10.1111/ctr.14060>

- Single center retrospective cohort study performed in the United States from 2007 to 2017 to determine how early post-transplant VA-ECMO or RVAD support impacts post-transplant outcomes.
- 30-day mortality occurred in 0.4% of the non-MCS group and in 44% of the MCS group. In hospital mortality occurred in 2% of the non-MCS group and in 56% of the MCS group. Patients who received VA ECMO support had a higher in-hospital mortality compared to the patients who received RVAD support (73% vs. 33%,  $p = 0.038$ ). Patients who did not receive MCS had better long-term survival compared to those who received MCS (1-year: 96%, 5-year: 89% vs. 1-year: 40%, 5-year: 22%). This difference in overall survival was not significant in a multivariate analysis ( $p = 0.22$ ).

Nagy A, et al. (2020). Perioperative low tetraiodothyronine levels and adverse outcomes after heart transplantation: A retrospective, observational study. *J Cardiothorac Vasc Anesth*, 34(10):2648-2654. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32389455/>

- Single center retrospective cohort study performed in Hungary from January 2015 to December 2019 to determine if perioperative T3 and T4 levels impact post-transplant outcomes.
- Low T4 levels are associated with increased risk for PGD ( $p < 0.001$ ) and associated with higher 30-day mortality compared to normal T4 levels. Decreased T3 and T4 levels together are associated with increased risk of PGD ( $p = 0.008$ ).

Peled Y, et al. (2020). Donor thyroid hormone therapy and heart transplantation outcomes: ISHLT transplant registry analysis. *J Heart Lung Transplant*, 39(10):1070-1078. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/32771439/>

- Multicenter retrospective cohort study using the International Society for Heart and Lung Transplantation Thoracic Transplant Registry from January 2006 to December 2016. The aim of this study was to determine if donor thyroid hormone (DTH) therapy is associated with early graft loss (EGL).
- Of the patients included in the study population, 68.8% had received a heart transplant from a donor who received TH supplementation. Patients in the DTH group had higher rates of EGL compared to the noDTH group (1.6% vs 1.1%,  $p = 0.015$ ), leading to death or retransplant due to graft failure within 48 hours of transplant. 30-day mortality was not significantly different between the two groups (4.4% vs 4.5%,  $p = .608$ ). 8-year survival was also not significantly different between the two groups ( $p = 0.14$ ).

Kinsella A, et al. (2020). Post-transplant survival in adult congenital heart disease patients as compared to dilated and ischemic cardiomyopathy patients; an analysis of the thoracic ISHLT registry. *Clinical Transplantation*, 34(9). Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32478908/>

- Adult heart transplant patients were analyzed from the ISHLT registry to evaluate survival outcomes of adult congenital heart disease (ACHD) specifically compared to ischemic (ICM) and dilated cardiomyopathy (DCM). In the 30,130 patients included, the one-year survival was 78.3% in ACHD, 84.3% in ICM, and 86.2% in DCM patients and they found that ACHD and ICM patients were at significantly higher mortality risk than DCM. Graft failure-related mortality was higher in the ACHD group within the first year of post-transplant as compared to DCM group, while there was no difference between groups in post year 1.

Nicoara A, et al. (2020). Association between primary graft dysfunction and acute kidney injury after orthotopic heart transplantation – a retrospective, observational cohort study. *Transp Int*, 33(8):887-894. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32299144/>

- Multicenter retrospective cohort study derived from UNOS data from January 1, 2009 to December 31, 2014 to determine if PGD is a risk factor for post-transplant acute kidney injury (AKI).
- Patients who developed more severe AKI after transplant (stages 2-3) were more likely to develop PGD requiring VAD support compared to those who developed no AKI or a less severe AKI (no/stage 1) (22.35% vs. 8.66%,  $p = 0.001$ ). In a multivariate analysis, independent factors associated with increased risk of developing stage 2-3 AKI included PGD requiring VAD, longer DBD duration, recipient pre-transplant serum creatinine, and recipient gender (male at higher risk).

Peled Y, et al. (2020). Donor thyroid hormone therapy is associated with an increased risk of graft dysfunction after heart transplantation. *Clin Transplant*, 34(7):e13887. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/32367594/>

- Single center retrospective cohort study performed in Israel from August 1997 to August 2018 to determine if thyroid hormone therapy in donors increases the risk of PGD in recipients after transplant.
- The donors who received T4 therapy had a higher incidence of PGD compared to the donors who did not receive T4 therapy (57.6% vs. 34.7%,  $p = 0.022$ ). PGD severity was also worse in donors who received T4 therapy (42% vs. 25% moderate/severe PGD,  $p = 0.007$ ). If the donor received T4 therapy and methylprednisolone, the incidence of PGD was not significantly different from the non-T4 donors (43% vs 34%,  $p = 0.341$ ). Recipients of donors who were treated with T4 therapy had a higher usage of inotropes after transplant (54% vs. 35%,  $p = 0.049$ ). In hospital and 30-day mortality did not significantly differ between the groups.

Nilsson J, et al. (2020). A nonrandomized open-label phase 2 trial of nonischemic heart preservation for human heart transplantation. *Nat Commun*, 11(1):2976. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/32532991/>

- Prospective, open-label, non-randomized trial performed in Sweden from April 2, 2017 to September 25, 2018 to determine if rates of primary graft dysfunction (PGD) were different between donor hearts using non-ischemic heart preservation (NIHP) compared to static cold preservation (SCS), which is currently used for donor hearts before transplantation. Six patients in the NIHP group and 25 in the SCS group due to limited availability of the technology to perform NIHP.
- At 6 months, 100% of the patients in the NIHP group achieved survival without severe PGD at 24 hours, without use of ECMO within 7 days, and without acute cellular rejection (ACR) of grade 2R or greater within 180 days; 72% of the SCS group achieved the same outcome.

Hoemann B, et al. (2020). Discontinuing amiodarone treatment prior to heart transplantation lowers incidence of severe primary graft dysfunction. *Clin Transplant*, 34(2):e13779. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/31903624/>

- Single center retrospective cohort study performed in the United States from January 2010 to June 2017 to determine if discontinuing amiodarone before transplant lowers the occurrence of severe PGD. There are 3 groups: Group 1 did not receive amiodarone, Group 2 received amiodarone continued to time of transplant, and Group 3 received amiodarone that was stopped before transplant.
- Only 1 of 42 patients (2.4%) in Group 3 was readmitted for new onset atrial fibrillation after amiodarone discontinuation. Difference in severe PGD was significantly different between the three groups: Group 1: 6.6%, Group 2: 25.4%, Group 3: 9.5% ( $p < 0.001$ ). Multivariate analysis showed that intraoperative packed red blood cell administration ( $p < 0.001$ ) and amiodarone continued to time of transplant ( $p = 0.018$ ) were risk factors for development of severe PGD. In-hospital mortality was not significantly different between the groups. One through four-year survival was not significantly different between the groups.

Peled Y, et al. (2020) Preoperative statin therapy and heart transplantation outcomes. *Annals Thorac Surg*. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/32156588>

- Retrospective cohort study comparing PGD incidence between heart transplant recipients who were on statin therapy during the month prior to and at the time of transplantation ( $n=167$ ) and those who were not ( $n=108$ )
- PGD was significantly lower among heart transplant recipients who received statin therapy prior to and at the time of heart transplantation (21 vs 60%,  $p < 0.001$ ).

Jennings DL, et al. (2017). Pre-cardiac transplant amiodarone use is not associated with postoperative mortality: An updated meta-analysis. *Int J Cardiol*. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28238350>

- Meta-analysis of the available evidence suggests that pre-operative amiodarone exposure does not increase mortality in cardiac transplant recipients.

Sabatino M, et al. (2017). Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: Epidemiology, risk factors, and outcomes. *J Heart Lung Transplant*. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28302502>

- Consensus-defined P-GD identifies patients at major risk for early death and graft loss after HT, although the "mild" grade appeared under-represented and clinically irrelevant. The amplified negative effect of donor and recipient factors on P-GD risk underscores the need for appropriate donor-recipient match

Lushaj EB, et al. (2016). To use or not to use? Amiodarone before heart transplantation. *Surgery*. [Epub ahead of print]. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27876282>

- Amiodarone use did not affect the incidence of atrial fibrillation nor 30-day and 1-year survival post-transplantation. Nevertheless, post-transplant pulmonary complications were significantly greater and 5-year survival was less among patients treated with amiodarone prior to transplant

Foster BJ, et al. (2015). High risk of graft failure in emerging adult heart transplant recipients. *Am J Transplant*, 15(12):3185-93. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26189336>.

- Crude age-specific graft failure rates were highest in 21-24 year olds (4.2 per 100 person-years). Compared to individuals with the same time since transplant, 21-24 year olds had significantly higher failure rates than all other age periods except 17-20 years (HR 0.92 [95%CI 0.77, 1.09]) and 25-29 years (0.86 [0.73, 1.03]). Among young first heart transplant recipients, graft failure risks are highest in the period from 17 to 29 years of age.

Morris AA, et al. (2015). Race and ethnic differences in the epidemiology and risk factors for graft failure after heart transplantation. *J Heart Lung Transplant*, 34(6):825-31. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25682551>

- Black HT recipients have the highest risk of GF, with immunologic factors conferring the greatest proportion of that risk. Racial differences in risk factors for GF after HT require further study.

## 5.6 Retransplantation

Zadikany RH, et al. (2021). Total artificial heart as bridge to cardiac retransplantation. *ASAIO J*, 68(3):e77-e79. Retrieved from: <https://doi.org/10.1097/mat.0000000000001217>

- Single center case study performed in the United States from January 2012 to June 2017. The purpose of this study was to review outcomes of patients who received therapy with total artificial heart (TAH) before retransplantation.
- Patient 1 experienced a *Pseudomonas* bacteremia that was thought to involve the TAH. This limited the desensitization treatment they were receiving. The other two patients experienced infections (*E. coli* pneumonia and *Enterobacter* bacteremia and bacterial pneumonia). They also experienced hemorrhagic stroke or recurrent GI bleeds.
- Patient 1 died shortly after retransplant due to bleeding and shock, thought to be related to the TAH-related infection. Patient 2 died after hemorrhagic stroke. Patient 3 was discharged 139 days after retransplantation after a complicated post-op course of GI bleeding and respiratory failure.

Zhu Y, et al. (2020). Outcomes after heart retransplantation: A 50-year single-center experience. *J Thorac Cardiovasc Surg*: S0022-5223(20)32145-0. Retrieved from: <https://doi.org/10.1016/j.jtcvs.2020.06.121>

- Single center retrospective cohort study performed in the United States from January 6, 1968 to June 2019. The aim of this study was to evaluate outcomes after retransplantation.
- Patients were more likely to need post-transplant dialysis compared to those who only received a primary transplant (21.4% vs 8.5%,  $p = 0.034$ ). Median survival after retransplant (4.6 years) compared to after primary transplant (9.9 years) was significantly different ( $p < 0.0001$ ). The hazard curve showed that patients who required retransplant within a year after their primary heart transplant were had the lowest rates of survival (median survival: 1-year: 0.2 years, 1-5 years: 3.7 years, >5 years: 7.5 years). All of the patients who needed a retransplant within 1 year of primary transplant were due to PGD.

Barghash MH and Pinney SP. (2020). Heart retransplantation: Candidacy, outcomes, and management. *Curr Transplant Rep*, 7(1):12-17. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32435573/>

- Review article that summarizes the incidence and epidemiology of retransplantation and to discuss the risk factors of poor outcomes after retransplantation.
- The most common indications for retransplantation are graft failure and CAV, with graft failure more common in first month after transplant and CAV more common after the first year of transplant.
- Short- and long-term survival are lower in patients who receive a retransplant compared to primary transplant recipients. 1-year survival for retransplantation is around 80% at 1-year compared to 85.4% for primary transplant. 5-year survival for retransplantation is 68.6% compared to 74.6% for primary transplant. Retransplantation within 1-year of primary transplant is associated with lower survival. Of the indications for retransplantation, CAV had the best 1-year survival at 74.7%, and primary graft failure had the worst 1-year survival at 54%.

Tjang TS, et al. (2008). Tenderich G, Hornik L, Korfer R. Cardiac retransplantation in adults: an evidence-based systematic review. *Thorac Cardiovasc Surg*, 2008; 56:323-327. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18704853>

- A systematic review of 22 published studies regarding cardiac retransplantation in adults

Johnson MR, et al. (2007) Heart retransplantation. *Am J Transplant*, 7:2075-2081. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17640316>

- A review article in which a working group developed recommendations, based on available data and expert opinion, concerning heart retransplantation.
- Summarized all relevant trials of retransplantation in adults and pediatrics
- One-, three-, and five-year unadjusted graft survival was lower in retransplants than in first transplants (82% vs. 86%, 70% vs. 80%, & 58% vs. 73%,  $p < 0.0001$ , respectively).

## 5.7 Heart Failure Etiologies and Management

### 5.7.1 Cardiomyopathy

Yamada T and Nomura S. (2021). Recent findings related to cardiomyopathy and genetics. *Int J Mol Sci*, 22(22):12522. Retrieved from: <https://dx.doi.org/10.3390%2Fijms222212522>



- This review provides a summary of the current genotype–phenotype correlations and latest findings on pathogenesis and drug discovery for dilated cardiomyopathy and hypertrophic cardiomyopathy.
- Recent evidence is discussed regarding other cardiomyopathies such as peripartum cardiomyopathy, cancer therapy-related cardiac dysfunction, and alcoholic cardiomyopathy, and the significance of common variants in cardiomyopathy.
- Clinical indications for genetic testing are provided along with the potential for use in precision medicine for dilated and hypertrophic cardiomyopathy and its importance for preventing the onset and progression of other cardiomyopathies, such as peripartum cardiomyopathy and cancer therapy-related cardiac dysfunction, and in healthy individuals with pathogenic variants of cardiomyopathy-related genes.

### 5.7.1.1 **Dilated Cardiomyopathy**

Cinq-Mars A, et al. (2021). Heavy burden of toxic dilated cardiomyopathy among young adults: a retrospective study and review of the literature. *Can J Cardiol*, S0829=8-282X(21)00823-0. Retrieved from: <https://doi.org/10.1016/j.cjca.2021.11.002>

- Single center retrospective cohort study performed in Canada from January 2003 to August 2019. This study aimed to evaluate outcomes in patients under 65 years with toxic dilated cardiomyopathy (TCM).
- Of the 201 patients with idiopathic dilated cardiomyopathy, 38 patients most likely had TCM. Within the TCM population 92% had more than one addiction. 50% used amphetamines, 37% used cocaine, 8% used anabolic-androgenic steroids, and 5% used energy drinks. During the follow-up period 68% completely stopped toxic consumption, 16% had one or more short relapse(s), and 16% could not stop consumption. Twenty-four percent of the study population needed cardiac resynchronization therapy. 18% needed an LVAD, and 3% needed ECMO. Patients with biventricular dysfunction had an event-free survival rate of 62.5% compared to 86.4% in patients who did not develop biventricular dysfunction ( $p < 0.05$ ).
- Seventy-one percent of patients ( $n=27$ ) had an event-free survival with guideline-directed therapy and 61% ( $n=23$ ) had an increased LVEF of 40% or greater after a median follow-up of  $21 \pm 23$  months.

Ebbesen MN, et al. (2021). Rate of heart failure following atrial fibrillation according to presence of family history of dilated cardiomyopathy or heart failure: a nationwide study. *J Am Heart Assoc*, 10(22):e021286. Retrieved from: <https://doi.org/10.1161/jaha.120.021286>

- Patients were identified through Danish nationwide registries and included those born after 1942 and diagnosed with atrial fibrillation from 2005 to 2015 and followed for 5 years. The aim of this study was to investigate the rate of developing heart failure (HF) in patients with atrial fibrillation with and without first-degree family members with HF or DCM.
- Seventeen percent of the study population had one or more family member(s) with HF/DCM. Having a family member with HF/DCM was associated with an increased 5-year risk of the composite of HF/death (cumulative incidence, 9.2% [95% CI, 7.8–10.7] versus 5.6% [95% CI, 5.0–6.1]; adjusted hazard ratio [HR] 1.36 [95% CI, 1.13–1.64]). (HF 8.4% [95% CI, 7.0–9.8] versus 4.5% [95% CI, 4.1–5.0]); (adjusted HR, 1.49 [95% CI, 1.22–1.82]). However, familial HF/DCM was not significantly associated with an increased 5-year risk and rate of death (0.8% [95% CI, 0.4–1.2] versus 1.1% [95% CI, 0.8–1.3]); (adjusted HR, 0.80 [95% CI, 0.46–1.39]).

- In patients with incident atrial fibrillation without prior ischemic heart disease or HF diagnosis, 1 of 6 had a first-degree relative with HF, and having such a family history of HF/DCM was associated with an 87% increase in 5-year incidence of HF compared with those without

Erdogan O, et al. (2021). A new biomarker that predicts ventricular arrhythmia in patients with ischemic dilated cardiomyopathy: Galectin-3. *Rev Port Cardiol (Engl Ed)*, 40(11):829-835. Retrieved from: <https://doi.org/10.1016/j.repce.2021.10.019>

- Single center retrospective cross-sectional study performed in Turkey from January 2017 to April 2017. The aim of this study was to determine if there was an association between ventricular arrhythmias and galectin-3 (Gal-3) in patients with ischemic dilated cardiomyopathy with an ICD.
- Ventricular arrhythmias requiring treatment occurred in 87.5% of the diabetic patients, whereas only 37.5% of the non-diabetic patients had an occurrence ( $p = 0.03$ ). Diabetic patients had higher Gal-3 levels when compared to non-diabetic patients (28.73 ng/mL vs. 12.54 ng/mL,  $p = 0.02$ ). Gal-3 levels were higher in patients with arrhythmias requiring ICD therapy compared to those with ICDs not requiring therapies (22.96 ng/mL vs. 10.70 ng/mL,  $p = 0.02$ ). Patients with arrhythmia storms had higher Gal-3 levels than those with no ICD therapies (26.79 ng/mL vs. 10.70 ng/mL,  $p = 0.05$ ). Gal-3 levels were not significantly different between patients with ICDs with arrhythmia storms vs. those with ICDs without arrhythmia storms (26.79 ng/mL vs. 16.84 ng/mL,  $p = 0.94$ ).
- ROC analysis showed 84% sensitivity and 75% specificity that Gal-3 levels  $>7$  ng/mL identifies ventricular arrhythmias requiring therapies.

Moeinafshar A, et al. (2021 Nov). Diagnostic biomarkers of dilated cardiomyopathy. *Immunobiology*, 226(6):152153. Retrieved from: <https://doi.org/10.1016/j.imbio.2021.152153>

- Review article that discusses the characteristics, epidemiology, etiology, and manifestations of DCM. It discusses the most important biomarkers for diagnosing DCM.

May BM, et al. (2021 Oct). Growth/differentiation factor-15 (GDF-15) as a predictor of serious arrhythmic events in patients with nonischemic dilated cardiomyopathy. *J Electrocardiol*, 70:19-23. Retrieved from: <https://doi.org/10.1016/j.jelectrocard.2021.10.002>

- Single center prospective study performed in Brazil from March 2011 to June 2016. The study's aim was to determine if GDF-15 was associated with serious arrhythmic events and mortality in patients with non-ischemic dilated cardiomyopathy.
- Serious arrhythmic events occurred in 19% of the study population. Of those, sudden cardiac death occurred in 61% of the arrhythmia patients. GDF-15 levels were not significantly different between the patients who developed arrhythmias vs. those who did not (1563 ng/L vs. 1270 ng/L,  $p = 0.14$ ). Study analysis determined that for every 30% increase in baseline GDF-15 level this was associated with an increased risk of ventricular arrhythmias or sudden cardiac death ( $p = 0.03$ ). Even in the adjusted analysis, GDF-15 was still a predictor of serious arrhythmia ( $p = 0.02$ ).
- GDF-15 levels were significantly higher in patients who died of any cause (1723 ng/L vs. 1183 ng/L,  $p < 0.001$ ). There was an increased risk of all-cause mortality with every 30% increase in serum GDF-15 level ( $p = 0.004$ )

Chen Y, et al. (2021). Outcomes of spironolactone withdrawal in dilated cardiomyopathy with improved ejection fraction. *Front Cardiovasc Med*, 8:725399. Retrieved from: <https://doi.org/10.3389/fcvm.2021.725399>

- Single center prospective cohort study performed in China from June 2016 to June 2017. The aim of this study was to determine the outcomes of spironolactone withdrawal in patients with improved LVEF in remission for DCM (n=70).
- Fifty-eight percent of the withdrawal group (n=23) and 13% of the continuation group (n=4) experienced relapse in DCM, leading to a relative risk for relapse after spironolactone withdrawal of 4.31 ( $p < 0.001$ ). More patients in the withdrawal group experienced aggravation of HF symptoms compared to the continuation group ( $p = 0.008$ ). The continuation group experienced continued ventricular remodeling, whereas the withdrawal group did not see any further remodeling after withdrawal.

Ivanov B, et al. (2021). Impact of ischaemic and dilated cardiomyopathy on short-term and long-term survival after ventricular assist device implantation: a single-centre experience. *Heart Lung Circ*, S1443-9506(21)01232-4. Retrieved from: <https://doi.org/10.1016/j.hlc.2021.08.017>

- Single center retrospective cohort study performed in Germany from February 2010 to December 2020. This study's aim was to determine the outcomes after LVAD implantation in patients with ICM (n=36) and DCM (n=24).
- DCM patients received a significantly higher number of Heartmate III LVADs ( $p < 0.001$ ). ICM patients had a higher number of additional cardiac procedures during LVAD implantation (36% ICM vs. 12% DCM,  $p = 0.052$ ). Post-op milrinone was significantly different between the groups (0.2 mcg/kg/min ICM vs. 0.25 mcg/kg/min DCM,  $p < 0.001$ ). In-hospital mortality and hospital length of stay were not significant between the groups ( $p = 0.206$ ,  $p = 0.349$ ). Though not significant, there was more pump thrombosis in patients with DCM ( $p = 0.080$ ). Study analyses showed that there were no significant differences in 90-day or long-term survival ( $p = 0.197$ ,  $p = 0.105$ ) based on etiology of heart failure.

Tayal U, et al. (2021). Moderate excess alcohol consumption and adverse cardiac remodeling in dilated cardiomyopathy. *Heart*, heartjnl-2021-319418. Retrieved from: <https://doi.org/10.1136/heartjnl-2021-319418>

- Multicenter prospective cohort study performed in the United Kingdom from 2009 to 2015. This study aimed to determine outcomes in DCM with moderate excess alcohol consumption, which they defined as 21 units/week in men or 14 units/week in women.
- Patients with DCM with a history of moderate excess alcohol consumption had more impaired cardiac phenotype (lower biventricular function, increased chamber dilation, and hypertrophy) compared to those without. Over a median follow up of 3.9 years, 13% experienced mortality, major HF event, or major cardiac event. Of those who experienced the primary endpoint, 19% had a history of moderate excess alcohol consumption, and 81% did not ( $p = 0.54$ ).
- Alcohol may contribute to sex-specific phenotypic differences in DCM.

Enzan N, et al. (2021). The use of angiotensin-converting enzyme inhibitors or angiotensin ii receptor blockers is associated with the recovered ejection fraction in patients with dilated cardiomyopathy. *Int Heart J*, 62(4):801-810. Retrieved from: <https://doi.org/10.1536/ihj.20-671>

- Multicenter prospective cohort study performed in Japan from 2003 to 2014. The aim of this study was to determine if DCM patients with HF with recovered EF was associated with ACEi/ARB use.
- The prevalence of LVEF of 40% or greater at 3 years in the ACEi/ARB group (57.0%) was higher than in the non-ACEi/ARB group (49.3%) ( $p = 0.002$ ). The prevalence of decreased LV diameter was higher in the ACEi/ARB group (57.1% vs 51.3%,  $p = 0.020$ ).

Enzan N, et al. (2021). Beta-blocker use is associated with prevention of left ventricular remodeling in recovered dilated cardiomyopathy. *J Am Heart Association*, 10(12):e019240. Retrieved from: <https://doi.org/10.1161/jaha.120.019240>

- Multicenter prospective case-matched study performed in Japan from 2003 to 2014. This study aimed to determine the outcomes of beta-blockers on LVEF in patients with recovered DCM.
- The prevalence of decrease in LVEF was lower in the beta-blocker group (19.6%) compared to the non-beta-blocker group (24.0%) ( $p = 0.013$ ). Prevalence of increase in LV diastolic diameter was lower in the beta-blocker group (11.7%) compared to the non-beta-blocker group (15.7%) ( $p = 0.008$ ). The beta-blocker group had less deterioration of LVEF  $< 40\%$  (24.2% vs 30.4%,  $p=0.003$ )
- Authors concluded that beta-blocker use could prevent deterioration of left ventricular systolic function in patients with recovered DCM.

Kim HM, et al. (2021). Beneficial effect of left ventricular remodeling after early change of sacubitril/valsartan in patients with nonischemic dilated cardiomyopathy. *Medicina (Kaunas)*, 57(5):416. Retrieved from: <https://doi.org/10.3390/medicina57050416>

- Single center retrospective cohort study performed in South Korea from January 2009 to November 2019. This study's aim was to determine if an early switch from ACEi/ARB to sacubitril/valsartan improved LVEF in patients with DCM.
- In patients who switched to sacubitril/valsartan within 60 days, the increase in LVEF and decrease in LV end-systolic diameter were more significant than those who switched later ( $p = 0.005$ ) and more significant than those who continued ACEi/ARB ( $p = 0.036$ ,  $p = 0.023$ ). There were no significant differences in clinical outcomes between the groups with regard to early/late switch to sacubitril/valsartan..

Fu L, et al. (2020). The impact of atorvastatin on cardiac performance for dilated cardiomyopathy: a meta-analysis of randomized controlled studies. *Heart Surg Forum*, 23(3):E329-E334. Retrieved from: <https://doi.org/10.1532/hcf.2787>

- A systematic review and meta-analysis of literature through February 2019 was performed to determine the influence of atorvastatin on cardiac performance in patients with dilated cardiomyopathy.
- The analysis found that LVEF was significantly increased in patients on atorvastatin ( $p < 0.00001$ ). In addition, atorvastatin was associated with a significantly improved positive impact on 6-minute walk test ( $p= 0.003$ ).

Kaya MG, et al. (2014). Evaluation of beta-blockers on left ventricular dyssynchrony and reverse remodeling in idiopathic dilated cardiomyopathy: A randomized trial of carvedilol and metoprolol. *Cardiology Journal*, 21(4):434-41.1. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24142686>

- Carvedilol was associated with greater reduction in LVEDV, increase in LVEF and improvement in inter-ventricular dyssynchrony compared to metoprolol. Both medications improved intraventricular dyssynchrony, reverse remodeling and BNP levels.

Braun M, et al. (2009). The calcium channel blocker felodipine attenuates the positive hemodynamic effects of the beta-blocker metoprolol in severe dilated cardiomyopathy--a prospective, randomized, double-blind and placebo-controlled study with invasive hemodynamic assessment. *International Journal of Cardiology*, 32, 248-256. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18579230>

- Patients receiving metoprolol experienced significantly improved LVEF, LVEDD as well as decreased PAP and PCWP. When combined with felodipine these benefits were negated.

### 5.7.1.2 Restrictive Cardiomyopathy

Griffin JM, et al. (2022). Surveillance for disease progression of transthyretin amyloidosis after heart transplantation in the era of novel disease modifying therapies. *The Journal of Heart and Lung Transplantation*. 2022;41(2):199-207. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34922822/>

- Single-center retrospective cohort study evaluated the incidence of *de novo* or progression of post-heart transplant (HT) advanced transthyretin (ATTR) deposition in patients transplanted due to advanced transthyretin cardiac amyloidosis (ATTR-CA). Among 12 patients included, 8 patients had symptoms of ATTR deposition at a median of 4.0 years post-HT. 4 patients had  $\geq 2$  body systems involved and no patient had recurrent cardiac involvement.

Jackson KC, et al. (2022). Heart transplantation outcomes in cardiac sarcoidosis. *J Heart Lung Transplant*, 41(1):113-122. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34756511/>

- Retrospective analysis using UNOS database that examined outcomes in patients with cardiac sarcoidosis. There was no difference in survival, graft failure, hospitalizations for infection, and post-transplant malignancy between patients with cardiac sarcoidosis and non-cardiac sarcoidosis. Patients with cardiac sarcoidosis had lower odds of rejection ( $p=0.0444$ ).

McGoldrick MT, et al. (2021). Long-term survival after heart transplantation for cardiac sarcoidosis. *J Card Surg*, 36(11):4247-4255. Retrieved from: <https://doi.org/10.1111/jocs.15783>

- Multicenter retrospective cohort study performed from UNOS database information from January 1, 1999 to March 20, 2020. The aim of this study was to evaluate post-transplant survival in patients with restrictive cardiomyopathy due to cardiac sarcoidosis (RCM-sarcoidosis).
- When compared to non-RCM indications for heart transplant, RCM-sarcoidosis was associated with reduced risk of mortality ( $p = 0.029$ ) whereas RCM due to other causes (RCM-other) was associated with an increased risk of mortality ( $p < 0.001$ ). One year survival between the RCM-sarcoidosis and non-RCM groups were similar (91.6% vs. 89.7%,  $p = 0.306$ ). Five year and 10-year survival were significantly higher in the RCM-sarcoidosis group compared to the non-RCM group (5-year: 87.7% vs. 77.2%,  $p = 0.004$ ; 10-year: 73.4% vs. 59.5%,  $p = 0.002$ ). One, 5, and 10 year survival were all significantly worse in the RCM-other group when compared to the non-RCM group ( $p = 0.001$ ). A multivariate regression showed that RCM-sarcoidosis was not associated with increased risk of CAD, stroke, need for pacemaker, ACR, infection, graft failure, or retransplantation.

Bistola V, et al. (2021). Practical recommendations for the diagnosis and management of transthyretin cardiac amyloidosis. *Heart Fail Rev*, 26(4):861-879. Retrieved from: <https://doi.org/10.1007/s10741-020-10062-w>

- Review article discussing the etiology, diagnosis, and management of ATTR-CM.

Sreenivasan J, et al. (2021). Left ventricular assist device implantation in hypertrophic and restrictive cardiomyopathy: a systematic review. *ASAIO J*, 67(3):239-244. Retrieved from:

<https://doi.org/10.1097/mat.0000000000001238>

- A systematic review of literature through May 2019 was performed to evaluate clinical outcomes of patients with LVAD due to hypertrophic cardiomyopathy (HCM) or restrictive cardiomyopathy (RCM) compared to those with dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM).
- Perioperative and short-term mortality were significantly higher in the HCM/RCM group (14.0%) compared to the DCM/ICM group (9.0%) ( $p < 0.001$ ). Post-op RV failure requiring inotrope

support was also higher in the HCM/RCM group compared to the DCM/ICM group (50.0% vs. 21.0%,  $p < 0.001$ ). The HCM/RCM group also had significantly more post-op complications: infection 15.5% vs. 11.2%, bleeding 40.2% vs. 12.5%, acute renal failure 15.0% vs. 5.1%, arrhythmias 18.0% vs. 7.7%, stroke 5.0% vs. 2.4% with all  $p$  values  $< 0.001$ .

Lamb YN. (2021). Tafamidis: a review in transthyretin amyloid cardiomyopathy. *Am J Cardiovasc Drugs*, 21(1):113-121. Retrieved from: <https://doi.org/10.1007/s40256-020-00461-7>

- A review article discussing the literature surrounding the safety and efficacy of tafamidis. It also discusses tafamidis dosing, administration, and niche in therapy.
- Tafamidis (Vyndaqel®, Vyndamax®) stabilizes transthyretin (TTR), which helps prevent the amyloidogenic misfolded TTR in ATTR cardiomyopathy. Tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations. Tafamidis was well-tolerated with few symptoms.
- Tafamidis is best used for symptom management in patients with ATTR-CM.

Michelis KC, et al. (2020). Durable mechanical circulatory support in patients with amyloid cardiomyopathy: insights from INTERMACS. *Circ Heart Fail*, 13(12):e007931. Retrieved from: <https://doi.org/10.1161/circheartfailure.120.007931>

- Multicenter retrospective cohort study derived from the INTERMACS database from June 2005 to December 31, 2017. The aim of this study was to determine the clinical outcomes of mechanical circulatory support (MCS) in patients with amyloid cardiomyopathy (ACM) [n=46] compared to dilated cardiomyopathy (DCM) [n=19,921] and nonamyloid restrictive cardiomyopathy (RCM) [n=248].
- Compared to patients with DCM and nonamyloid RCM, patients with ACM had a higher mortality with heart transplant ( $p = 0.014$ ), and ACM was associated with a 2.5-fold increased risk of death compared to DCM ( $p < 0.001$ ). When comparing device types, ACM patients with LVADs were the only group that showed increased risk of death when compared to DCM or nonamyloid RCM patients with LVADs ( $p < 0.001$ ), but there was no significant difference with the groups who received biventricular MCS. Patients with ACM had the highest mortality risk among the groups both with bridge to transplant ( $p = 0.002$ ) and for destination therapy ( $p < 0.001$ ). The ACM group also saw more major bleeding ( $p = 0.005$ ), neurological dysfunction ( $p = 0.006$ ), hemorrhagic CVA ( $p = 0.006$ ), and renal dysfunction ( $p < 0.001$ ) compared to DCM and nonamyloid RCM groups.
- Data included in this study highlight concerns with the use of durable MCS for patients with ACM.

Barrett CD, et al. (2020). Outcomes in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation. *JACC Heart Fail*, 8(6):461-468. Retrieved from: <https://doi.org/10.1016/j.jchf.2019.12.013>

- Single center retrospective cohort study (n=31) performed in the United States from 2004 to 2017. The purpose of this study was to evaluate outcomes in patients with cardiac amyloidosis after transplant.
- Post-transplantation, there were no differences in post-operative bleeding, renal failure, infection, rejection, or malignancy between the AL amyloidosis group (n=13) and the ATTR amyloidosis group (n=18). Also, there was no significant difference in survival between amyloid and non-amyloid cardiomyopathy patients who received a transplant.

Sousa M, et al. (2017). Heart transplantation in cardiac amyloidosis. *Heart Fail Rev*, 22(3):317-27.. 2017 Mar 9. doi: 10.1007/s10741-017-9601-z. [Epub ahead of print] Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28281017>

- Cardiac amyloidosis and heart transplantation review article

Rosenbaum AN, Edwards BS. (2015) Current indications, strategies, and outcomes with cardiac transplantation for cardiac amyloidosis and sarcoidosis. *Curr Opin Organ Transplant*. 2015 Oct;20(5):584-92. doi:10.1097/MOT.0000000000000229. Retrieved at: <https://pubmed.ncbi.nlm.nih.gov/26262459/>

- Outcomes after heart transplantation are typically worse than in patients undergoing heart transplantation for nonamyloid disease. This review analyzes the indications, strategies and outcomes in patients with amyloidosis and sarcoidosis.

### **5.7.1.3 Infectious Cardiomyopathy**

Schultheiss HP, et al. (2021). Viral myocarditis-from pathophysiology to treatment. *J Clin Med*, 10(22):5240. Retrieved from: <https://doi.org/10.3390/jcm10225240>

- A review article that discusses the pathophysiology, diagnosis, and treatment of viral myocarditis.

Echeverría LE, et al. (2021). Survival after heart transplantation for Chagas cardiomyopathy using a conventional protocol: A 10-year experience in a single center. *Transpl Infect Dis*, 23(4):e13549. Retrieved from: <https://doi.org/10.1111/tid.13549>

- Single center retrospective cohort study performed in Colombia from January 2008 to July 2018. The aim of this study was to determine the outcomes of 43 patients with Chagas cardiomyopathy (CCM) who underwent transplant. This center used MMF without benznidazole prophylaxis or RT-PCR follow up to look for parasite burden. They relied on microscopic examination and identification of parasites or tissue sample evidence of parasitic infection to evaluate Chagas infection reactivation.
- Survival in the study population was 74.66%, with the most common causes of death being infection and rejection complications. Rejection was the most common complication (60.46%). Fifty percent of the population had more than one episode of rejection and 50% needed treatment for their rejection episode. Infection complications occurred in 44.18% of patients, with respiratory tract infections being the most common. Sixty percent of the patients died due to infection. T. cruzi reactivation occurred in 3 patients. All 3 patients were treated with benznidazole, which resulted in remission and no fatalities.

Holanda MT, et al. (2021). Effects of selenium treatment on cardiac function in chagas heart disease: Results from the STCC randomized Trial. *EClinicalMedicine*, 40:101105. Retrieved from: <https://doi.org/10.1016/j.eclinm.2021.101105>

- Single center, prospective, double-blinded, placebo-controlled, phase-3 randomized controlled trial performed in Brazil from May 2014 to September 2018. The purpose of this study was to determine the safety and efficacy of selenium treatment in chronic Chagas cardiomyopathy (CCC).
- There were no significant differences in LVEF changes between the selenium and placebo groups at 6 months ( $p = 0.51$ ) or at 12 months ( $p = 0.23$ ). At one year follow-up, most of the cases remained in the same stage of CCC (75.8% in the placebo group vs. 87.1% in the selenium group). There were no significant differences in CCC staging changes between the two groups. There were no significant differences in adverse drug reactions between the selenium and placebo groups ( $p = 0.82$ ).

Benatti RD, et al. (2017). Heart transplantation for chagas cardiomyopathy. *J Heart Lung Transplant*. 36(6):597-603. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28284779>

- Chagas cardiomyopathy (CC) and heart transplantation review article

#### 5.7.1.4 Peripartum Cardiomyopathy

Kwon JH, et al. (2022). Heart transplantation for peripartum cardiomyopathy: outcomes over three decades. *Ann Thorac Surg*, S0003-4975(22)00066-2. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35085525/>

- Retrospective analysis using UNOS database evaluating trends and outcomes of patients undergoing heart transplantation for peripartum cardiomyopathy (PPCM). Among females, PPCM was associated with significantly elevated one-year mortality compared to non-ischemic cardiomyopathy ( $p=0.004$ ) and worse early and mid-term survival compared with other HF diagnoses ( $p<0.001$ ). However, survival improved significantly in the last decade for patients transplanted for PPCM ( $p<0.001$ ), particularly for black recipients.

Iorgoveanu C, et al. (2021). Peripartum cardiomyopathy: a review. *Heart Fail Rev*, 26(6):1287-1296. Retrieved from: <https://doi.org/10.1007/s10741-020-10061-x>

- A review of peripartum cardiomyopathy that describes the epidemiology, pathophysiology, risk factors, diagnosis, and management through different periods of pregnancy in patients with PCCM

Trongtorsak A, et al. (2021). Effects of bromocriptine in peripartum cardiomyopathy: a systematic review and meta-analysis. *Heart Fail Rev*. Retrieved from: <https://doi.org/10.1007/s10741-021-10185-8>

- A systematic review and meta-analysis evaluating literature through June 2021. The purpose of this study was to determine if bromocriptine impacts the outcomes of patients with peripartum cardiomyopathy (PPCM).
- Therapy with bromocriptine was associated with a higher rate of survival compared to no bromocriptine therapy in patients with PCCM (92.6% vs. 83.9%,  $p = 0.02$ ). Bromocriptine was associated with a higher increase in LVEF compared to the non-bromocriptine group (29.5-53.3% vs. 31.8-41.8%,  $p = 0.05$ ).

Badianyama M, et al. (2021). A systematic review of the utility of bromocriptine in acute peripartum cardiomyopathy. *Cureus*, 13(9):e18248. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8475739/pdf/cureus-0013-00000018248.pdf>

- A systematic review of literature from July 10, 2001 to July 10, 2021. The aim of this study was to evaluate the safety and efficacy of combining bromocriptine with conventional HF treatment in patients with PCCM.
- Mean LVEF was significantly improved in all of the studies included in this analysis. Mean LVEF was higher in patients on bromocriptine therapy (58% vs. 36%,  $p = 0.0007$ ; 49.9 vs 40.9,  $p = 0.001$ ). LVEF was improved in 92% of patients on bromocriptine in one study vs. 72% not on bromocriptine. In other studies, LVEF was improved by 11.37% and 15.14% in the bromocriptine groups ( $p = 0.001$  and  $p = 0.0006$ , respectively). Of the studies included in the review, there was a significantly different number of deaths in the bromocriptine group vs. the non-bromocriptine group (16.6% vs. 29.1%,  $p = 0.0001$ ; 16% vs. 31%,  $p = 0.07$ ).

Djordjevic I, et al. (2021). The outcome of patients with peripartum cardiomyopathy and consecutive implantation of a left ventricular assist device. *J Card Surg*, 36(8):2651-2657. Retrieved from:

<https://doi.org/10.1111/jocs.15598>

- Multicenter retrospective cohort study derived from the EUORMACS database from May 2011 to September 2018. This study's aim was to determine the outcomes of patients with LVAD due to PCCM ( $n=16$ ).
- Most patients in this study population received an LVAD as a bridge to transplant (69%) compared to a few who received LVAD as a means to recovery (13%). In-hospital mortality was



6% (n=1) and 1-year mortality was 13% (n=2). One patient died due to intracranial bleeding and one died due to pump thrombosis and device malfunction.

- The authors concluded that durable mechanical support should be considered as a treatment option for severe PCCM allowing for potential bridging to heart transplant or left ventricular recovery.

Karaye KM, et al. (2020). Selenium supplementation in patients with peripartum cardiomyopathy: A proof-of-concept trial. *BMC Cardiovasc Disord*, 20(1):457. Retrieved from: <https://doi.org/10.1186/s12872-020-01739-z>

- Open-label randomized controlled trial performed in Nigeria from June 12, 2017 to December 1, 2017. The purpose of this study was to evaluate the efficacy and safety of selenium in patients with PCCM and selenium deficiency.
- Selenium levels were higher in both the selenium group and non-selenium group from baseline compared to last follow-up (49.8 mcg/L vs. 85.2 mcg/L, 48.1 mcg/L vs. 74.5 mcg/L, respectively,  $p < 0.001$ ). Selenium levels did not differ significantly between the groups by the end of the study ( $p = 0.073$ ). HF symptoms, LVEF  $< 55\%$ , or death occurred in 78.3% of the selenium group and 79.6% of the non-selenium group ( $p = 0.113$ ). There were no serious adverse effects with selenium therapy.

Achmad C, et al. (2020). T-peak to T-end improvements after beta-blocker administration in peripartum cardiomyopathy patients. *Cardiol Res*, 11(3):185-191. Retrieved from: <https://doi.org/10.14740/cr1053>

- A single center prospective cohort study performed in Indonesia from 2014 to 2016 that included 34 patients. The purpose of this study was to determine if beta-blocker therapy can improve T-peak to T-end (TPTE) interval to decrease outcomes of sudden cardiac death. TPTE has been shown to be associated with sudden cardiac events.
- After 6 months of beta-blocker therapy, mean LVEF in the study population was 58.26% (increased from mean LVEF of 32.24% at baseline). Mean TPTE was 98.7 ms after 6 months of beta-blocker therapy (decreased from 123.7 ms at baseline). There was a significant difference between TPTE at baseline and 6-months after beta-blocker therapy ( $p < 0.001$ ).

Sinkey RG, et al. (2020). Racial disparities in peripartum cardiomyopathy: eighteen years of observations. *J Matern Fetal Neonatal Med*, 1-8: Retrieved from: <https://doi.org/10.1080/14767058.2020.1773784>

- A single center retrospective cohort study performed in the United States from January 2000 to November 2017 that included 46 black women and 49 white women. The aim of this study was to evaluate outcomes in patients with PCCM of different races to determine if there were any disparities between groups.
- White patients with PCCM were more likely to have private insurance compared to black women with PCCM (79.6% vs. 34.8%,  $p < 0.0001$ ). Black women were more likely to deliver earlier than white women (36.5 weeks gestation vs. 38.5 weeks gestation,  $p = 0.02$ ). Almost all diagnoses of PCCM were post-partum vs. antepartum in both groups (95.4% in black women, 93% in white women,  $p = 0.11$ ). Ejection fraction (EF) at diagnosis of PCCM was not different between black and white women (26.8% vs. 28.7,  $p = 0.41$ ). Months from diagnosis to recovery did not differ significantly between the groups ( $p = 0.28$ ). In all EF groups, black women were more likely to have LV systolic dysfunction remaining at 6-12 months ( $p = 0.0002$ ,  $p = 0.0006$ , and  $p = 0.04$ ). Five black women and 3 white women died during the course of the study ( $p = 0.48$ ). Medication use (GDMT) was similar between the groups, and no patients received bromocriptine therapy. Black women were more likely to have emergency room visits, inpatient admissions, and ICU admissions ( $p < 0.01$ ,  $p = 0.01$ , and  $p = 0.005$ ).

Westhoff-Bleck, M. et al (2013). Cardiovascular disorders in pregnancy: diagnosis and management. *Best Practice & Research Clinical Obstetrics and Gynaecology*, 27, 821-834. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23932772>

- Summary of pathophysiology, diagnosis and treatment of cardiovascular disorders during pregnancy, including peri-partum cardiomyopathy.

Lund, LH, et al (2011). Myocardial recovery in peri-partum cardiomyopathy after continuous flow left ventricular assist device. *Journal of Cardiothoracic Surgery*, 6: 150. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22082339>

- Case report of peri-partum cardiomyopathy requiring LVAD that recovered and remains stable in NYHA class I-II 18 months post-explantation.

Rasmusson, KD (2007). Long-term outcomes of cardiac transplantation for peri-partum cardiomyopathy: a multiinstitutional analysis. *Journal of Heart and Lung Transplantation*, 26, 1097-1104. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18022074>

- Sixty-nine women who received a heart transplant for peri-partum cardiomyopathy (PPCM) were compared to males as well as females with and without history of pregnancy. Risk of rejection was greater for the PPCM group compared to males and females without previous pregnancy. Long-term survival for PPCM recipients was comparable to males and improved compared to other females.

#### **5.7.1.5 Right Ventricular Cardiomyopathy**

Tu B, et al. (2021). Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers: anti-arrhythmic drug for arrhythmogenic right ventricular cardiomyopathy. *Front Cardiovasc Med*, 8:769138. Retrieved from: <https://doi.org/10.3389/fcvm.2021.769138>

- A single center retrospective cohort study performed in China from October 2001 to November 2017 that included 311 patients. The purpose of this study was to determine if the use of ACEi/ARB therapy impacts outcomes in arrhythmogenic right ventricular cardiomyopathy (ARVC).
- TAPSE (tricuspid annular plane systolic excursion) decreased by 0.61 mm/year in the non-ACEi/ARB group, whereas the decrease in TAPSE was slower in the ACEi/ARB group at 0.24 mm/year ( $p < 0.001$ ). Comparing the medication classes, ACEi therapy was associated with a slower decrease in TAPSE by 70% when compared to ARBs ( $p = 0.026$ ). With mild RV dysfunction, decrease in TAPSE was slower in the ACEi/ARB group compared to the non-ACEi/ARB group (0.37 mm/year vs 0.61 mm/year,  $p < 0.001$ ).
- 65.3% of patients in the study population experienced a life-threatening ventricular arrhythmia event. Analysis revealed that the factors associated with increased rate of life-threatening ventricular arrhythmias included younger age, male sex, higher burden of 24 hour premature ventricular contractions, recorded non-sustained VT, lower TAPSE, lower RVEF, and higher burden of RV-LGE%. Patients in the ACEi/ARB group experienced less life-threatening ventricular arrhythmia events than the non-ACEi/ARB group (55.8% vs. 71.2%,  $p = 0.013$ ). There was a reduced risk of sustained VT in the ACEi/ARB group as well (53.5% vs. 63.8%,  $p = 0.017$ ).

Ren J, et al. (2020). Plasma testosterone and arrhythmic events in male patients with arrhythmogenic right ventricular cardiomyopathy. *ESC Heart Fail*, 7(4):1547-1559. Retrieved from: <https://doi.org/10.1002/ehf2.12704>

- A single center retrospective cohort study performed in China from October 2015 to July 2018 that included 99 patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and 96

control patients. The purpose of this study was to determine if testosterone levels play a role in major cardiac events in patients with ARVC.

- Plasma testosterone levels were higher in patients who experienced a malignant arrhythmic event, and it was determined an independent factor associated with malignant arrhythmic events ( $p < 0.001$ ).

Ermakov S, et al. (2014). Combination drug therapy for patients with intractable ventricular tachycardia associated with right ventricular cardiomyopathy. *Pacing and Clinical Electrophysiology*, 37, 90-94.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24102153>

- Review of four RV cardiomyopathy cases with RV-originating ventricular arrhythmia refractory to monotherapy and/or ablation. Combination therapy with sotalol, flecainide and mexiletine was used to control arrhythmia.

### 5.7.2 Congenital heart disease

Batsis M, et al. (2021). Association of digoxin with preserved echocardiographic indices in the interstage period: a possible mechanism to explain improved survival? *J Am Heart Assoc*, 10(23):e021443.

Retrieved from: <https://doi.org/10.1161/jaha.121.021443>

- A multicenter retrospective cohort study performed in the United States from 2005 to 2008. The aim of this study was to evaluate the effect of digoxin on RV indices post stage 1 palliation in infants with single ventricle congenital heart disease.
- After the Norwood procedure, there were no statistical differences between the RV end-diastolic volume, RV end-systolic volume, or ejection fraction between the digoxin and non-digoxin groups.
- The authors concluded that digoxin use during the interstage period is associated with better preservation of RV volume and tricuspid valve measurements leading to less adverse remodeling of the single ventricle. These findings suggest a possible mechanism of action explaining digoxin's survival benefit during the interstage period.

Donovan DJ, et al. (2021). Association between homograft tissue exposure and allosensitization prior to heart transplant in patients with congenital heart disease. *Pediatr Transplant*, e14201. Retrieved from:

<https://doi.org/10.1111/petr.14201>

- A single center retrospective cohort study performed in the United States from January 1, 2011 to March 31, 2018. The aim of this study was to determine the association between pre-sensitization prior to heart transplant and exposure to homograft tissue in patients with congenital heart disease.
- Patients who received homografts before transplant were more likely to be pre-sensitized (defined by PRA >10%) (OR=7.31,  $p = 0.007$ ), and to have developed any anti-HLA antibody at various levels, >0 (OR = 4.52,  $p = .034$ ), >2000 (OR = 8.59,  $p = .003$ ), and >6000 (OR=8.50,  $p = .004$ ). Patients who were pre-sensitized were more likely to have longer exposure to homograft tissue (9.80 vs. 4.96 years,  $p = 0.025$ ).

Assenza GE, et al. (2021). AHA/ACC vs ESC Guidelines for Management of Adults With Congenital Heart Disease: JACC Guideline Comparison. *J Am Coll Cardiol*, 78(19):1904-1918. Retrieved from:

<https://doi.org/10.016/j.jacc.2021.09.010>

- A review article summarizing and comparing/contrasting the AHA/ACC and ESC guidelines for adult congenital heart disease.

de la Rosa AL, et al. (2021). Advanced heart failure and heart transplantation in adult congenital heart disease in the current area. *Clin Transplant*, 35(11):e14451. Retrieved from:

<https://doi.org/10.1111/ctr.14451>

- A single center retrospective cohort study performed in the United States from January 1, 2010 to December 31, 2020. The aim of this study was to evaluate outcomes in patients transplanted for adult congenital heart disease (ACHD).
- The rates of desensitization were not statistically significant between the ACHD and non-ACHD groups (21.1% vs. 13.2%,  $p = 0.46$ ). Within the first year of transplant, patients with ACHD were more likely to be treated for ACR (21.1% vs. 15.8%,  $p = 0.010$ ) and AMR (15.8% vs. 10.5%,  $p = 0.033$ ). Mortality at 30-days, at 1-year, and at median follow-up of 3.3. years were not significant between the groups ( $p = 0.26$ ,  $p = 0.21$ ,  $p = 0.36$ , respectively).

Hong KN, et al. (2021). Cardiac transplantation in danon disease. *J Card Fail*, S1071-9164(21)00466-8.

Retrieved from: <https://doi.org/10.1016/j.cardfail.2021.11.007>

- Danon disease is an X-linked dominant mutation that causes severe cardiomyopathy, which is often fatal without heart transplant.
- A multicenter retrospective study performed in Spain, Italy, and the United States from December 29, 1985 to May 19, 2020. The aim of this study was to determine post-transplant outcomes in patients with Danon disease (DD) who received a heart transplant.
- Three of the 38 patients with DD experienced a stroke prior to transplant. Also, there were 2 deaths and 2 retransplants. Five-year graft survival was 87.1%. In patients who survived to discharge there was one episode (2.7%) of antibody-mediated rejection, grade 2, and 7 episodes (19%) of acute cellular rejection, grade 2 or 3,

Huang ST, et al. (2021). Effect of postoperative administration of inhaled nitric oxide combined with high-frequency oscillatory ventilation in infants with acute hypoxemic respiratory failure and pulmonary hypertension after congenital heart surgery: A retrospective cohort study. *J Card Surg*. 1-7. Retrieved from:

<https://doi.org/10.1111/jocs.16163>

- A single center retrospective cohort study performed in China from January 2020 to March 2021. The purpose of this study was to determine the impact of inhaled nitric oxide (iNO) combined with high-frequency oscillatory ventilation (HFOV) in patients with acute hypoxemic respiratory failure (AHRF) and pulmonary hypertension (PH) after congenital heart surgery.
- The oxygenation index (OI) in patients with HFOV and iNO was improved more significantly than in the HFOV group at 6, 12, 24, and 48 hours ( $p = 0.046$ ,  $p = 0.034$ ,  $p = 0.048$ , and  $p = 0.046$ , respectively).  $\text{PaO}_2$  was significantly better at 6 and 12 hours in the HFOV and iNO group vs. HFOV group ( $p = 0.049$  and  $p = 0.047$ , respectively). The HFOV group had significantly longer duration of mechanical ventilation 7.0 days vs. 5.6 days). ICU length of stay was shorter in the HFOV and iNO group (9.9 days vs. 12.8 days). Hospital length of stay was not significantly different between the groups.

Kainuma A, et al. (2021). Changes in waitlist and posttransplant outcomes in patients with adult congenital heart disease after the new heart transplant allocation system. *Clin Transplant*, 35(11):e14458.

Retrieved from: <https://doi.org/10.1111/ctr.14458>

- A multicenter retrospective cohort study derived from the UNOS database from January 2010 to March 2020. The purpose of this study was to determine waitlist and post-transplant outcomes in adult patients with CHD. The allocation policy changed in October 2018 awarding an exception status to patients with ACHD because these patients were previously the lowest priority for heart transplant.

- There were no significant differences in the before policy change vs. the after policy change with regards to early complications or 1-year survival ( $p = 0.791$ ). Compared to patients waitlisted in the pre-policy change era, those waitlisted in the post policy change era were more likely to receive transplants ( $P = .001$ ) with no significant difference in waiting list mortality ( $P = .267$ ) or delisting ( $P = .915$ ).

Lammers AE, et al. (2021). Ventricular assist devices in paediatric cardiomyopathy and congenital heart disease: An analysis of the German National Register for Congenital Heart Defects. *Int J Cardiol*, 343:37-44. Retrieved from: <https://doi.org/10.1016/j.ijcard.2021.08.047>

- A multicenter retrospective cohort study performed in Germany from March 1999 to November 2015. The aim of the study was to evaluate outcomes in patients who received a VAD due to cardiomyopathy or CHD.
- Patients with CM were more likely to receive a transplant after VAD support compared to those with CHD (79.5% vs. 28.0%,  $p < 0.0001$ ). Mortality was higher in the CHD group at 48.0% compared to the CM group at 17.9% ( $p < 0.0001$ ). There was no significant difference in mortality after transplant between the CM and CHD groups ( $p = 0.24$ ). Patients with CHD did have a higher mortality rate than those with CM ( $p < 0.0001$ ).
- Independent predictors of mortality in CHD patients included a diagnosis of CHD (hazard ratio [HR] 4.04,  $p = 0.001$ ), age at VAD implantation (HR 1.09/year,  $p = 0.04$ ) and the need for pre-VAD extracorporeal membrane oxygenation (ECMO) support (HR 3.23,  $p = 0.03$ ).

O'Connor MJ, et al. (2021). Center variation in indication and short-term outcomes after pediatric heart transplantation: analysis of a merged united network for organ sharing – pediatric health information system cohort. *Pediatr Cardiol*. Retrieved from: <https://doi.org/10.1007/s00246-021-02768-x>

- A multicenter retrospective cohort study derived from UNOS and PHIS databases from January 1, 2004 to March 31, 2015. The purpose of the study was to evaluate post transplant outcomes.
- Thirty day mortality after transplant in CHD, myocarditis, and CM were 5.5%, 2.9%, and 1.1%, respectively ( $p < 0.0001$ ). Hospital length of stay differed between the CHD, myocarditis, and CM groups (25 days, 20 days, and 16 days,  $p < 0.0001$ ). Comprehensive hospital length of stay including readmissions within a year from transplant, were also significantly different between the CHD, myocarditis, and CM groups (34 days, 28 days, and 22 days, respectively;  $p < 0.0001$ ).

Rochelson E, et al. (2021). Sotalol versus amiodarone for postoperative junctional tachycardia following congenital heart surgery. *Heart Rhythm*, S1547-5271(21)02354-7. Retrieved from: <https://doi.org/10.1016/j.hrthm.2021.11.021>

- A single retrospective cohort study ( $n=32$ ) performed in the United States from December 15, 2015 to December 15, 2020. The aim of this study was to determine the safety and efficacy of IV sotalol vs. IV amiodarone for postoperative junctional ectopic tachycardia (JET).
- Amiodarone was successful in treating JET in 75% of cases; sotalol was successful in 83%. The JET rate decreased faster over the first 90 minutes after a sotalol bolus (25 beats/min per hour) than after an amiodarone bolus (8 beats/min per hour) ( $P < .01$ ); no heart rate difference was seen after 24 hours. Amiodarone infusion was discontinued early because of hypotension/bradycardia in 2 patients; this was not required in any patients receiving sotalol.
- The authors concluded that for children with postoperative JET, both IV sotalol and amiodarone are safe and efficacious. IV sotalol may lead to a faster improvement in heart rate.

Shah MJ, et al. (2021). 2021 PACES Expert Consensus Statement on the Indications and Management of Cardiovascular Implantable Electronic Devices in Pediatric Patients: Developed in Collaboration With and Endorsed by the Heart Rhythm Society (HRS), the American College of Cardiology (ACC), the

American Heart Association (AHA), and the Association for European Paediatric and Congenital Cardiology (AEPC) Endorsed by the Asia Pacific Heart Rhythm Society (APHRs), the Indian Heart Rhythm Society (IHRS), and the Latin American Heart Rhythm Society (LAHRS). *JACC Clin Electrophysiol*, 7(11):1437-1472. Retrieved from: <https://doi.org/10.1016/j.jacep.2021.07.009>

- This document provides guidelines for cardiovascular implantable electronic device use, management, and follow up in pediatric patients.

Das BB, et al. (2021). Contemporary outcomes of durable ventricular assist devices in adults with congenital heart disease as a bridge to heart transplantation. *Artif Organs*. Retrieved from: <https://doi.org/10.1111/aor.14092>

- A multicenter retrospective cohort study derived from the UNOS thoracic transplantation database from January 1, 2010 to December 31, 2019. The aim of this study was to compare the clinical characteristics, risk factors, and overall survival outcomes in adults with congenital heart disease (ACHD) bridged to transplantation with a ventricular assist device (VAD) versus no-VAD.
- Waitlist mortality was 38% in the VAD group vs. 17% in the non-VAD group ( $p < 0.01$ ). There were no significant differences in the percentage of patients who made it to transplant between the VAD and no-VAD groups ( $p = 0.21$ ). At the time of transplant, there was a higher need for inotropic support in the no-VAD group compared to the VAD group. One year mortality between the groups was not significantly different (15% in VAD group vs. 17% in no-VAD group,  $p = 0.66$ ).
- The authors concluded that the study findings suggest that a VAD should be considered an option to support ACHD patients as a bridge to heart transplantation.

Heid CA, et al. (2021). Cardiac transplantation in adults with congenital heart disease: A single center case series. *Clin Transplant*, 35(10):e14430. Retrieved from: <https://doi.org/10.1111/ctr.14430>

- A single center retrospective case series performed in the United States from January 1, 2013 to July 30, 2020. The purpose of this study was to determine the outcomes of patients with CHD who underwent a transplant.
- Operative times and cardiopulmonary bypass times were longer in the CHD group compared to the non-CHD group (7.5 hours vs. 5.6 hours,  $p < 0.001$ ; 197 minutes vs. 130 minutes,  $p < 0.001$ ). Outcomes (including ejection fraction, ICU readmission, length of ICU stay, adverse cardiac events, and length of hospital stay) were all non-significant between the CHD and non-CHD groups.

Khan A, et al. (2021). Improved heart transplant survival for children with congenital heart disease and heterotaxy syndrome in the current era: An analysis from the pediatric heart transplant society. *J Heart Lung Transplant*, 40(10):1153-1163. Retrieved from: <https://doi.org/10.1016/j.healun.2021.07.008>

- A multicenter retrospective cohort study derived from the Pediatric Heart Transplant Society (PHTS) database from January 1, 1993 to December 31, 2018. The purpose of this study was to evaluate outcomes after transplant in patients with congenital heart disease with heterotaxy syndrome (CHD-HS) compared to other types of CHD.
- There were no significant differences in waitlist outcomes of transplant, death, or removal due to deterioration between the CHD-HS group and the other CHD group ( $p = 0.7$ ,  $p = 0.8$ ,  $p = 0.3$ , respectively). One year survival was 77.2% in the CHD-HS group compared to 85.1% in the CHD group ( $p < 0.01$ ). Five year survival was 66.4% in the CHD-HS group and 75.4% in the CHD group ( $p < 0.01$ ). Single ventricle heart disease was an early mortality risk factor for patients with CHD. CHD-HS patients had a lower freedom from infection and from severe rejection, but no difference in vasculopathy or malignancy.

Krishnan GS, et al. (2021). Heart transplantation for patients with single ventricle physiology. *Indian J Thorac Cardiovasc Surg*, 37(6):647-661.. Retrieved from: <https://doi.org/10.1007/s12055-021-01241-x>

- A single center retrospective observational study performed in India from October 2012 to October 2019. The purpose of this study was to determine if post-transplant outcomes differed in patients with a single ventricle.
- Early mortality was 25%, one-year survival was 75%, and five-year survival was 63%. Survival and length of hospital stay were not significantly different between patients with single ventricle physiology compared to those with normal ventricle physiology.

Lu Y, et al. (2021). Favorable outcomes after heart transplantation in Barth syndrome. *J Heart Lung Transplant*, 40(10):1191-1198. Retrieved from: <https://doi.org/10.1016/j.healun.2021.06.017>

- Barth syndrome (BTHS) is an X-linked disorder that causes cardioskeletal myopathy and neutropenia.
- A multicenter retrospective cohort study was performed with patients obtained from the Pediatric Health Information Systems (PHIS)-Scientific Registry of Transplant Recipient (SRTR) dataset from North America, the United Kingdom, and Brazil from 2002 to 2016. The aim of this study was to determine post-transplant outcomes in patients with BTHS who have received a heart transplant.
- There were no significant differences in post-transplant survival between the BTHS and non-BTHS groups ( $p = 0.92$ ). There were no significant differences in the two groups with regards to freedom from PTLD/malignancy ( $p = 0.18$ ) and CAV ( $p = 0.41$ ). Patients in the BTHS group had greater freedom from acute rejection compared to non-BTHS group ( $p = 0.02$ ). The BTHS group also had fewer acute rejection episodes in the first year compared to the non-BTHS group ( $p = 0.02$ ).

Butto A, et al. (2021). Relationship of ventricular assist device support duration with pediatric heart transplant outcomes. *J Heart Lung Transplant*, S1053-2498(21)02521-3. Retrieved from: <https://doi.org/10.1016/j.healun.2021.09.011>

- A multicenter retrospective cohort study derived from the Pediatric Heart Transplant Study (PHTS) database before 2000. The aim of this study was to determine if patients with less than 30 days of VAD support had different outcomes compared to patients with 30 days or greater of VAD support.
- One-year survival was significantly different between the groups at 89.8% survival in the <30 day group and 93.9% in the  $\geq 30$  day group ( $p = 0.016$ ). Children with CHD had worse survival compared to children with CM or myocarditis. There were no significant differences in rejection or infections between the two VAD groups.

Scott M and Neal AE. (2021). Congenital heart disease. *Prim Care*, 48(3):351-366. Retrieved from: <https://doi.org/10.1016/j.pop.2021.04.005>

- A review article that discusses etiology of congenital heart diseases (CHDs), diagnosis of CHDs, and care for CHDs, including care into adulthood.

Kearney K, et al. (2021). Waitlist and post-transplant outcomes for Eisenmenger syndrome: A comparison of transplant strategies. *J Heart Lung Transplant*, 40(8):841-849. Retrieved from: <https://doi.org/10.1016/j.healun.2021.04.005>

- A multicenter retrospective cohort study derived from the International Society for Heart and Lung Transplantation (ISHLT) registry from October 1, 1987 to March 31, 2018. The purpose of this study was to determine outcomes on the transplant waitlist for patients with Eisenmenger

syndrome due to atrial septal defect (ES-ASD) vs. patients with ES due to ventricular septal defect (ES-VSD). The study also aimed to compare long-term outcomes in patients with ES treated with a lung transplant with cardiac repair vs. a heart/lung transplant (HLTxp).

- In the early period of the study (1983 to 2004), ES-ASD patients who received a HLTxp had better survival compared to those who received a lung transplant (LTxp) with cardiac repair ( $p = 0.026$ ). In the late period of the study (2005-2018), ES-ASD patients who received a LTxp with cardiac repair had better survival compared to those with HLTxp ( $p = 0.016$ ). In the early period, ES-VSD patients who received a HLTxp had better survival compared to those with LTxp with cardiac repair ( $p = 0.016$ ). In the late period, ES-VSD patients had no significant difference in survival between the two groups ( $p = 0.214$ ).

Dolgner SJ, et al. (2021). Long-term adult congenital heart disease survival after heart transplantation: A restricted mean survival time analysis. *J Heart Lung Transplant*, 40(7):698-706. Retrieved from: <https://doi.org/10.1016/j.healun.2021.02.019>

- A multicenter retrospective cohort study derived from the UNOS database from January 2000 to December 2019. The purpose of this study was to evaluate if patients with ACHD had different outcomes after transplant compared to non-ACHD patients.
- In the matched cohorts, the ACHD group had an 18-year graft survival of 41.4% vs. 38.2% in the non-ACHD group ( $p = 0.02$ ). Average graft survival times were 11.14 years in the ACHD cohort and 11.40 years in the non-ACHD cohort ( $p = 0.38$ ). Patients in the ACHD group had a higher risk for early mortality ( $p < 0.001$ ).

Huntley GD, et al. (2021). Donor characteristics and recipient outcomes after heart transplantation in adult congenital heart disease. *J Am Heart Assoc*, 10(14):e020248. Retrieved from: <https://doi.org/10.1161/jaha.120.020248>

- A multicenter retrospective cohort study derived from the Scientific Registry of Transplant Recipients (SRTR) from 2000 to 2016. The aim of this study was to determine if outcomes after transplant are impacted by donor characteristics or waitlist times in patients with ACHD.
- Thirty day survival was worse for patients with ACHD vs. non-CHD ( $p < 0.001$ ), but 4-year survival was similar between the groups ( $p = 0.31$ ). Greater than 4 year survival was better in the ACHD group compared to the non-CHD group ( $p < 0.001$ ). There were no donor factors associated with early or intermediate mortality in patients with ACHD. However, the study showed that pre-recovery steroid use, meeting high-risk donor criteria, and heart rate were all associated with increased late mortality ( $p = 0.006$ ). The diagnosis of ACHD was associated with a waitlist time of 69.5 days longer than patients with non-ACHD.

Diamant MJ, et al. (2021). No survival benefit associated with waiting for non-lung donor heart transplants for adult recipients with congenital heart disease. *Clin Transplant*, 35(5):e14266. Retrieved from: <https://doi.org/10.1111/ctr.14266>

- A multicenter retrospective cohort study derived from the UNOS registry from January 1, 1987 to December 31, 2016. The purpose of this study was to evaluate post-transplant outcomes in adult patients with CHD who received a non-lung donor (NLD) compared to those with concomitant lung donors.
- There was no significant difference in waitlist times between recipients of NLD vs. concomitant lung donors (254 days vs. 278 days,  $p = 0.31$ ). There was no significant difference in 1-year mortality between the groups ( $p = 0.08$ ).



Riggs KW, et al. (2021). Transplantation for congenital heart disease: focus on the impact of functionally univentricular versus biventricular circulation. *World J Pediatr Congenit Heart Surg*, 12(3):352-359.

Retrieved from: <https://doi.org/10.1177/2150135121990650>

- A multicenter retrospective cohort study derived from the UNOS and PHIS databases from 2006 to 2017. The aim of this study was to determine if single ventricle patients with CHD had different outcomes compared to biventricular patients with CHD.
- Single ventricle patients had higher sensitization (36.0% vs 26.7%,  $p = 0.010$ ). However, single ventricle patients were less likely to need ECMO or VAD support at transplant (ECMO use 5.0% vs. 10.3%,  $p < 0.001$ ; VAD use 4.7% vs. 11.5%,  $p < 0.001$ ). There was no significant difference in survival between the two groups ( $p = 0.893$ ).

Kainuma A, et al. (2021). Cardiac transplantation in adult congenital heart disease with prior sternotomy. *Clin Transplant*, 35(4):e14229. Retrieved from: <https://doi.org/10.1111/ctr.14229>

- A single center retrospective cohort study performed in the United States from January 2008 to December 2018. The purpose of this study was to determine early and long-term outcomes in ACHD patients with a prior sternotomy.
- There was no significantly different 10-year survival between patients with ACHD and patients without ACHD ( $p = 0.429$ ). There was no significant difference in 10-year survival between the single ventricle and biventricular groups ( $p = 0.467$ ).

de Miguel IM and Ávila P. (2021). Atrial fibrillation in congenital heart disease. *Eur Cardiol*, 16:e06.

Retrieved from: <https://doi.org/10.15420/ecr.2020.41>

- A review article discussing the epidemiology, pathophysiology, clinical impact, and management of atrial fibrillation in adults with congenital heart disease.

Baumgartner H, et al. (2021). 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*, 42(6):563-645. Retrieved from: <https://doi.org/10.1093/eurheartj/ehaa554>

- An update of the guidelines for adult congenital heart disease between 2010 to 2020.

Freisinger E, et al. (2020). Current use and safety of novel oral anticoagulants in adults with congenital heart disease: results of a nationwide analysis including more than 44,000 patients. *Eur Heart J*, 41(43):4168-4177. Retrieved from: <https://doi.org/10.1093/eurheartj/ehaa844>

- A multicenter retrospective cohort study derived from the BARMER database in Germany from 2005 to 2018. The aim of this study was to determine long-term safety and efficacy of NOACs vs. VKAs in ACHD patients.
- Within 1 year of new anticoagulation, 9.5% of ACHD patients required hospitalization for bleeding and 15.5% required hospitalization within the first 2 years of anticoagulation. Bleeding rates in the first year were higher in patients on NOACs (11.5%) vs. VKAs (8.8%) ( $p = 0.001$ ). There was no difference between the groups after the first year of anticoagulation. Major thromboembolic events occurred more frequently in ACHD patients on NOACs (3.7%) vs. VKAs (2.8%) in the first year and in the second year (6.4% vs. 4.7%) ( $p < 0.05$  in both years). There were also a higher number of major adverse cardiovascular events in ACHD patients on NOACs compared to VKAs ( $p < 0.05$ ). All cause mortality was higher in the NOAC group compared to the VKA group at both 1 year (4.0% vs. 2.8%) and 2 years (6.8% vs. 5.0%) ( $p < 0.05$ ).

Perrotta ML, et al. (2020). Adults with mild-to-moderate congenital heart disease demonstrate measurable neurocognitive deficits. *J Am Heart Assoc*, 9(19):e015379. Retrieved from:

<https://doi.org/10.1161/jaha.119.015379>

- A multicenter retrospective cohort study derived from the UK Biobank registry in the United

Kingdom. The purpose of this study was to determine the impact of acquired CV disease on the outcomes of neurocognitive function in patients with mild/moderate CHD.

- In all 6 neurocognitive exams, the ACHD group had significantly worse performance in 3/6 tests and worse performance in 6/6 tests compared to the non-ACHD group. The ACHD group had 5 times the occurrence of stroke compared to the non-ACHD group ( $p < 0.001$ ).

VanderPluym, C et al. (2013). Advanced therapies for congenital heart disease: ventricular assist devices and heart transplantation. *Canadian Journal of Cardiology*, 29, 796-802. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/23683470>

- This article reviews reasons for VAD implantation in congenital heart disease (CHD), VAD support in Fontan circulation, challenges with human leukocyte antigen sensitization in heart transplantation (HT), and the effect of VAD support on HT in CHD.

Pincott, SE et al. (2011). Indications for heart transplantation in congenital heart disease. *Current Cardiology Reviews*, 7, 51-58. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22548027>

- This article reviews the indications for transplantation in congenital heart disease, the timing of transplantation, as well as potential complications of transplantation in congenital heart disease.

McGlothlin, D et al. (2011). Transplantation in adults with congenital heart disease. *Progress in Cardiovascular Diseases*, 53, 312–323. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21295673>

- This article addresses some of the unique challenges to transplantation and post-transplant management in congenital heart disease.

Hosseinpour, A et al. (2006). Transplantation for adults with congenital heart disease. *European Journal of Cardio-thoracic Surgery*, 30, 508–514. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16857376>

- This article reviews indications for transplantation in congenital heart disease and addresses unique considerations and complications to transplant.

### **5.7.3 Valvular heart disease**

Melgaard L, et al. (2021). Effectiveness and safety of noac versus warfarin in patients with atrial fibrillation and aortic stenosis. *J Am Heart Assoc*, 10(23):e022628. Retrieved from:

<https://doi.org/10.1161/jaha.121.022628>

- A multicenter retrospective cohort study derived from 4 different Danish nationwide registries from 2013 to 2018. The purpose of this study was to determine thromboembolic and bleeding outcomes in patients on NOACs vs. warfarin due to atrial fibrillation (AF) with aortic stenosis.
- Three year thromboembolic-free survival was similar between the NOAC and warfarin groups (94.0% vs. 96.0%). Three year survival free from major bleeds was 87.6% in the NOAC group and 83.6% in the warfarin group.

Izumi C, et al. (2021). Antithrombotic therapy for patients with atrial fibrillation and bioprosthetic valves – real-world data from the multicenter, prospective, observational BPV-AF registry. *Circ J*. Retrieved from:

<https://doi.org/10.1253/circj.cj-21-0564>

- A multicenter, prospective, observational study derived from the BPV-AF registry from September 2018 to October 2019. The aim of this study was to evaluate efficacy and safety of DOACs, warfarin, and antiplatelets in patients with atrial fibrillation (AF) and bioprosthetic valves (BPV).
- The event rate for stroke or systemic embolism was 2.10%/year (95% CI, 1.22–3.61) in warfarin-treated patients and 1.48%/year (95% CI, 0.62–3.55) in DOAC-treated patients. The event rate for major bleeding was 1.77%/year (95% CI, 0.98–3.20) in warfarin-treated patients and

2.08%/year (95% CI, 0.99–4.36) in DOAC-treated patients.. There were no significant differences in stroke or systemic embolism or major bleeding event rates between warfarin- and DOAC-treated patients (log-rank P=0.500 and P=0.746, respectively).

Vahanian A, et al. (2021). 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*, 00:1-72. Retrieved from: <https://doi.org/10.1093/eurheartj/ehab395>

- An update to the previous 2017 guidelines which includes patient evaluation, risk stratification, and management.

Huda SA, et al. (2021). Management of life-threatening bleeding in patients with mechanical heart valves. *Cureus*, 13(6):e15619. Retrieved from: <https://doi.org/10.7759/cureus.15619>

- A review article discussing the management of major bleeding events in patients with mechanical heart valves.

Kobari Y, et al. (2021). Aspirin versus clopidogrel as single antithrombotic therapy after transcatheter aortic valve replacement: insight from the OCEAN-TAVI registry. *Circ Cardiovasc Interv*, 14(5):e010097. Retrieved from: <https://doi.org/10.1161/circinterventions.120.010097>

- A multicenter retrospective cohort study derived from the OCEAN-TAVI registry in Japan from October 2013 to May 2017. The purpose of this study was to evaluate the outcomes of aspirin vs. clopidogrel after transcatheter aortic valve replacement..
- All-cause deaths were not statistically different between the groups in patients with (aspirin, 17.5%; clopidogrel, 11.1%; log-rank P=0.07) and without (aspirin, 29.6%; clopidogrel, 20.1%; log-rank P=0.15) anticoagulation at 2 years after TAVR, whereas clopidogrel was associated with a lower cardiovascular mortality at 2 years in patients with (aspirin, 8.5%; clopidogrel, 2.7%; log-rank P=0.03) and without (aspirin, 18.0%; clopidogrel, 5.2%; log-rank P=0.02) anticoagulation.
- There were no significant differences in 2-year incidence of major bleeding or stroke between the groups. The all-cause death rate at 2 years was higher in the warfarin group than in the DOAC group in patients on aspirin (warfarin, 28.0%; DOAC, 5.5%; P=0.002), while it was not different in patients on clopidogrel (warfarin, 9.8%; DOAC, 12.8%; P=0.70).

Otto CM, et al. (2021). 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, 143(5):e35-e71. Retrieved from: <https://doi.org/10.1161/cir.0000000000000932>

- An updated guideline providing recommendations for the diagnosis and management of valvular heart disease.

Nishimura RA, et al. (2017). AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *Circulation*, 135: e1159–e1195. Retrieved from: <https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000503>

- Guidelines published by American College of Cardiology (ACC) and the American Heart Association (AHA) on treatment of patients with heart valve disorders, such as evaluation of patients with heart murmurs, prevention and treatment of endocarditis, management of valve disease in pregnancy, and treatment of patients with concomitant coronary artery disease (CAD), as well as more specialized issues that pertain to specific valve lesions.

Baumgartner H, et al. (2017). ESC/EACTS Guidelines for the management of valvular heart disease. *European Heart Journal*, 38(36): 2739–91. Retrieved from: <https://academic.oup.com/eurheartj/article/38/36/2739/4095039>

- Guidelines published by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) on management of valvular heart disease

#### 5.7.4 **LVAD pre-transplant**

Jain R, et al. (2022). De novo human leukocyte antigen allosensitization in heartmate 3 versus heartmate ii left ventricular assist device recipients. *ASAIO Journal*. 2022;68(2):226-232. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33883507/>

- Retrospective chart review investigated the differential effect of HM3 implantation on HLA allosensitization in comparison to HMII. Development of high-level (MFI >10,000) antibodies was significantly lower in HM3 than HMII patients (p=0.049). Fewer HM3 patients had a positive PRA than HMII patients (p=0.015). Among transplanted patients, those who had developed *de novo* sensitization on LVAD support showed a trend toward incidence of moderate to severe grade rejection compared with unsensitized patients (p=0.078).

Srinivasan AJ, et al. (2022). Recent changes in durable left ventricular assist device bridging to heart transplantation. *ASAIO Journal*. 2022;68(2):197-204. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33788800/>

- Retrospective analysis using the UNOS database evaluated the impact of the recent UNOS allocation policy change on outcomes of patients bridged with durable left ventricular assist devices (LVADs) to orthotopic heart transplantation (OHT). OHT following durable LVAD bridging decreased from 45% to 34% (p < 0.001). Patients in the new-policy cohort were at higher risk due to more extracorporeal membrane oxygenation bridging, more mechanical right ventricular support, greater pretransplant ICU admission, more need for total functional assistance, older donor age, and longer ischemic times. However, early post-OHT survival was comparable at 30 days, 90 days, and 6 months.

Lambadaris M, et al. (2022). Association between continuous-flow left ventricular assist device infections requiring long-term antibiotic use and post-heart transplant morbidity and mortality. *J Card Surg*, 37(1):96-104. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34651943/>

- Single-center retrospective observational cohort study. Among 75 LVAD patients, 21% had chronic LVAD-related infection on suppressive antibiotics, 40% had resolved infection, and 39% had no infections. LVAD patients with infections did not have a significantly higher risk of infection, rejection, or mortality at any time point after transplant.

Immohr MB, et al. (2021). Impact of pre-transplant left ventricular assist device support duration on outcome after heart transplantation. *Interact Cardiovasc Thorac Surg*, ivab265. Retrieved from: <https://doi.org/10.1093/icvts/ivab265>

- A single center, prospective study performed in Germany between 2010 and 2021. The aim of this study was to determine if LVAD implantation impacts subsequent heart transplant outcomes. Study participants were separated into groups based on how long they required LVAD support before transplant (Group 1: <90 days, Group 2: 90 days to 1 year, Group 3: 1 to 2 years, Group 4: >2 years).
- The study showed no difference in graft ischemia time, post-operative hospital length of stay, or ICU length of stay. The study did show that time requiring mechanical ventilation differed between

groups (group 2 = 49 hours, group 3 = 103 hours). Groups 2 and 3 had significantly different incidences of severe primary graft dysfunction that required VA-ECMO (25.8% vs. 41.4%). There were no statistically significant differences between the groups with regard to perioperative severe adverse events. There were also no statistically different rates of acute graft rejection between patients who received LVAD support for a short duration (Group 1 = 28.6%), intermediate duration (Group 2 = 3.3%, Group 3 = 7.1%), and long duration (Group 4 = 12.5%) [P=0.06].

- Duration of LVAD support did not have an impact on 30-day survival ( $p = 0.48$ ) or on 1-year survival ( $p = 0.74$ ).

King PM, et al. (2020). Right heart failure while on left ventricular assist device support is associated with primary graft dysfunction. *ASAIO J*, 66(10):1137-1141. Retrieved from:

<https://doi.org/10.1097/mat.0000000000001156>

- A single center retrospective cohort study performed in the United States from 2009 to 2016. The aim of this study was to determine the post-transplant outcomes in patients with right heart failure (RHF) requiring LVAD.
- 43.9% of the RHF group developed primary graft dysfunction (PGD), whereas only 14.0% of the non-RHF group developed PGD ( $p < 0.001$ ). Thirty day mortality (19.5% vs. 1.0%) and 1-year mortality (22.0% vs. 6.0%) were significantly higher in the RHF group ( $p < 0.001$ ,  $p = 0.013$ , respectively).
- The authors concluded that the results of this study showed that patients supported with LVADs who develop early severe RHF or late RHF were at increased risk of PGD and death following cardiac transplantation.

Lescroart M, et al. (2020). Pulsatility in ventricular assistance devices: A translational review focused on applied haemodynamics. *Arch Cardiovasc Dis*, 113(6-7):461-472. Retrieved from:

<https://doi.org/10.1016/j.acvd.2020.03.017>

- A review article discussing pulsatility and LVADs to understand physiopathology and adverse effects of continuous-flow devices.

DeFilippis EM, et al. (2021). ECMO as a Bridge to Left Ventricular Assist Device or Heart Transplantation. *JACC Heart Fail*, 9(4):281-289. Retrieved from: <https://doi.org/10.1016/j.jchf.2020.12.012>

- A multicenter retrospective cohort study derived from the UNOS database from 2006 to June 2019. The aim of this study was to compare outcomes between patients on ECMO as a bridge to LVAD and patients on ECMO as a bridge to heart transplant (HT).
- Patients bridged to transplant were more likely to have non-ischemic and restrictive cardiomyopathies ( $p < 0.001$ ). Patients bridged to LVAD had a longer hospital length of stay compared to those bridged to transplant ( $p = 0.004$ ). Patients bridged to LVAD were more likely to be on IV inotrope therapy ( $p < 0.001$ ). Study analysis showed no significant difference in mortality when bridged to LVAD or bridged to transplant ( $p = 0.100$ ). Of the patients bridged to transplant, mortality was 29.3% at 1 year, 33.4% at 2 years, and 38.2% at 5 years. Of the patients bridged to LVAD, mortality was 30.8% at 1 year, 37.4% at 2 years, and 43.5% at 5 years.
- The authors concluded that there was no difference in mortality on pump support compared with posttransplant mortality among those bridged from ECMO to LVAD or HT.

Miller RJH, et al. (2020) Transplant outcomes in destination therapy left ventricular assist device patients. ASAIO. 2020 Apr; 66(4):394-8. doi: 10.1097/MAT.0000000000001016. Retrieved at: <https://www.ncbi.nlm.nih.gov/pubmed/31192848>

- There was no significant difference in 1-year survival or survival time between heart transplant recipients who had LVADs implanted as bridge-to-transplant (BTT) versus destination therapy (DT) prior to transplantation. Post-transplantation non-fatal adverse events were also similar between both treatment groups.

Truby LK, et al. (2020) Impact of induction immunosuppression on post-transplant outcomes of patients bridged with contemporary left ventricular assist devices. ASAIO. 2020 Mar; 66(3):261-7. doi: 10.1097/MAT.0000000000001119. Retrieved at: <https://www.ncbi.nlm.nih.gov/pubmed/32101996>

- There was no significant difference in the primary outcomes of graft survival, freedom from hospitalization for rejection, and freedom from hospitalization for infection between BTT LVAD patients who received induction therapy (IT) and those who did not. There was also no significant difference in freedom from hospitalization for infection among transplant recipients who had an infected LVAD prior to transplantation. LVAD patients who received IT had increased freedom from transplant coronary artery disease (TCAD), with increased freedom from TCAD among those who received antithymocyte globulin compared to basiliximab.

Grimm JC, et al. (2016) Duration of left ventricular assist device support does not impact survival after US heart transplantation. Ann Thorac Surg. 2016; 102(4):1206-12. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27319984>

- In the largest, non-industry sponsored study of a modern bridge to transplant cohort, this study demonstrated that duration of LVAD support before orthotopic heart transplantation does not influence posttransplant morbidity or mortality. In subanalysis, support for 90 days or more is associated with improvements in pretransplant functional performance.

Healy AH, et al. (2016) Predictors of 30-day post-transplant mortality in patients bridged to transplantation with continuous-flow left ventricular assist devices--An analysis of the International Society for Heart and Lung Transplantation Transplant Registry. J Heart Lung Transplant. 2016 Jan;35(1):34-9. doi: 10.1016/j.healun.2015.07.007.Epub 2015 Jul 29. Retrieved at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4629696/>

- In patients supported with continuous flow LVADs, risk factors for early mortality can be identified before transplant, including ventilator support, female recipient/male donor, increasing recipient age, and body mass index. Despite the inherent complexities of a reoperative surgery, patients bridged to transplant with CF LVADs have excellent peri-operative survival.

Ko BS, et al. (2016) Immunologic effects of continuous-flow left ventricular assist devices before and after heart transplant. J Heart Lung Transplant. 2016 Aug; 35(8):1024-30. doi: 10.1016/j.healun.2016.05.00. Epub 2016 May 6. Retrieved at: <https://www.ncbi.nlm.nih.gov/pubmed/27316382>

- Following continuous flow LVAD implantation, 23% of patients became allosensitized (defined as cPRA >10% in patients with pre-implantation cPRA of ≤10%). There was a higher risk of ACR and AMR among those who were bridged to heart transplantation with continuous flow LVAD compared to those who were not.

Kidambi S, et al. (2015) Clinical outcomes in sensitized heart transplant patients bridged with ventricular assist devices. *Clin Transplant*. 2015 Jun;29(6):499-505. doi: 10.1111/ctr.12540. Epub 2015 Apr 30.

Retrieved at: <https://pubmed.ncbi.nlm.nih.gov/25773536/>

- Sensitization appears to have a negative effect on mortality. This mortality appears to be concentrated in patients with AMR, and the authors postulate that the development of AMR in a sensitized patient may be a predictor of mortality.

## 5.8 Pre-transplant Considerations

Jimenez DC, et al. (2022). Cardiac transplantation after heparin-induced thrombocytopenia: A systematic review. *Clinical Transplantation*. 2022;36(2). Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34927287/>

- Systematic review included 33 patients from 21 studies who had clinical diagnosis of Heparin-induced thrombocytopenia (HIT) and required heart transplantation (HTx). Intraoperatively, 61% of patients were given unfractionated heparin (UFH), while 39% were given alternative anticoagulants. The alternative agent subgroup required more antifibrinolytics ( $p = 0.02$ ) and clotting factors ( $p < 0.01$ ). Perioperative thrombosis occurred more in the alternative agent subgroup ( $p < 0.01$ ). More patients in the alternate agent subgroup required post-operative transfusions ( $p < 0.01$ ). Thirty-day mortality was comparable between the subgroups.

O'Connell G, et al. (2022). Impact of UNOS allocation policy changes on utilization and outcomes of patients bridged to heart transplant with intra-aortic balloon pump. *Clinical Transplantation*. 2022;36(2).

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34786769/>

- Retrospective UNOS database review of heart transplant candidates with intra-aortic balloon pumps (IABPs) listed or transplanted before and after the UNOS policy changes. Patients with IABPs listed after the policy change were more likely to receive a transplant and were transplanted more quickly ( $p < 0.001$ ). Post-transplant survival was comparable before and after the policy change ( $p = 0.056$ ), but non-transplanted patients were more likely to be delisted post-policy change ( $p < 0.001$ ).

Finnan MJ, et al. (2022). 30 years of heart transplant: outcomes after mechanical circulatory support from a single center. *Ann Thorac Surg*, 113(1):41-48. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/33675715/>

- Single-center retrospective review of OHT patients from 1988 to 2019. Primary transplantation rates declined from 88% to 14% over the course of the study as the use of MCS increased. Survival of patients treated with continuous-flow LVAD and temporary MCS was noninferior to that of primary transplantation ( $p=0.22$ ). There was no major difference in postoperative complications based on pretransplantation MCS status.

Carter KT, et al. (2022). Venoarterial extracorporeal membrane oxygenation is a viable option as a bridge to heart transplant. *J Thorac Cardiovasc Surg*, 163(1):140-147.e4. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/32928549/>

- Retrospective analysis using UNOS database that analyzed restricted mean survival time. OHT recipients bridged with mechanical support and those without support were compared to recipients bridged with ECMO. Restricted mean survival time was higher in patients who did not require mechanical support (16.6 months), LVAD (16.5 months), IABP (11.2 month), and biventricular assist device (6.6 months) when compared with recipients who received ECMO. Restricted mean survival time was similar to ECMO in patients with RVAD or total artificial heart.

Wayda B, et al. (2021). Optimal patient selection for simultaneous heart-kidney transplant: A modified cost-effectiveness analysis. *Am J Transplant*. Retrieved from: <https://doi.org/10.1111/ajt.16888>

- Multicenter retrospective cohort study and cost-effectiveness analysis in the United States from 2014 to 2018. This study compared those who received a simultaneous heart-kidney transplant (SHK) to those who received transplants using the Safety Net strategy, where patients received a heart transplant, and then received a kidney transplant 6 months later if their natural kidneys did not recover after the heart transplant.
- The analysis showed that patients with low probability of kidney recovery after heart transplant used more kidneys and had slightly poorer survival with both strategies compared to other patients. However, these patients received greater reduction in 1-year mortality with the SHK strategy compared to the Safety Net strategy.
- The analysis showed that patients with moderate to high probability of kidney recovery after heart transplant benefit more with the Safety Net strategy across all outcomes.

Melvinsdottir I, et al. (2020). Heart and kidney transplant: Should they be combined or subsequent? *ESC Heart Fail*, 7(5):2734-2743. Retrieved from: <https://doi.org/10.1002/ehf2.12864>

- Multicenter retrospective cohort study performed using UNOS data from January 1, 2001 to December 31, 2016. This study aimed to determine if outcomes differed between patients who received a heart and kidney transplant (HKTx) compared to a kidney transplant after heart transplant (KAH).
- The study analysis showed that patients in the HKTx group (with or without dialysis) had a higher risk for death compared to patients in the KAH group ( $p = 0.001$ ). Cause of death differed between the groups, with the major causes of death in the HKTx group being bacterial infection, malignancy, cardiac arrest, and multiple organ failure, and with the major causes of death in the KAH group being kidney failure, malignancy, or unknown cause of death.

Dhakal BP, et al. (2020). Relation of pretransplant peak oxygen consumption to outcomes after heart transplantation. *Am J Cardiol*, 127:52-57. Retrieved from: <https://doi.org/10.1016/j.amjcard.2020.04.022>

- Multicenter retrospective cohort study from the United States from January 2000 to December 2015. This study aimed to determine if pre-transplant peak exercise oxygen consumption ( $pVO_2$ ) have an impact on post-heart transplant outcomes. The study participants were divided into groups B ( $pVO_2$  16-20 mL/kg/min), C ( $pVO_2$  10 - <16), and D ( $pVO_2$  <10) depending on their pre-transplant  $pVO_2$ .
- Post-transplant survival decreased with decreasing  $pVO_2$  (B – 92% 1 year, 80% 5 year; C – 90% 1 year, 79% 5 year; D – 87% 1 year, 75% 5 year;  $p < 0.001$ ). With decreasing  $pVO_2$ , there was also a decreasing median survival time (B – 13.6 years; C – 12.8 years; D – 11.4 years). The analysis showed that with every 1 mL/kg/min increase in  $pVO_2$ , there was an association of a 2% decrease in mortality in the 1 year, 5 year, and overall follow up ( $p < 0.001$  for all three follow up times).

Giordanino EF, et al. (2020). Short-term mechanical circulatory support devices as bridge to heart transplantation: A prospective single-center experience in Argentina. *Clin Transplant*, 34(7):e13888. Retrieved from: <https://doi.org/10.1111/ctr.13888>

- Single center prospective cohort study performed in Argentina from April 2006 to April 2018. The aim of this study was to determine if use of ECMO or centrifugal pump (CP) before transplant as a bridge to therapy impacted outcomes after transplant.



- The main adverse event from short-term mechanical circulatory support devices (ST-MCS) during ST-MCS therapy was AKI (54.1%), bleeding (35.1%), and vasoplegic syndrome (35.1%). Patients on CP therapy were at higher risk for AKI, bleeding, and mortality compared to those on ECMO.
- Of the patients who survived ST-MCS to transplant, 14/30 were on ECMO before transplant, and 16/30 were on CP before transplant. Of these patients, 26.7% developed moderate/severe PGD requiring intra-aortic balloon pump (IABP) or ST-MCS. Of the 30 patients, 60% developed AKI after transplant, and 43.3% developed vasoplegic syndrome. There was no significant difference between ICU length of stay or hospital length of stay between the ECMO and CP groups. There was also no difference in 30-day or 4-year survival between the two groups.

Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J Heart Lung Transplant*. 2016 Jan;35(1):1-23. doi: 10.1016/j.healun.2015.10.023. Retrieved at: <https://pubmed.ncbi.nlm.nih.gov/26776864/>

- Review of heart transplant listing criteria

## 5.9 Post-transplant Considerations

Shoji S, et al. (2022). Incidence and long-term outcome of heart transplantation patients who develop postoperative renal failure requiring dialysis. *J Heart Lung Transplant*, 41(3):356-364. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34953720/>

- Retrospective analysis using the UNOS database included 28,170 patients, of which 3,371 (12%) required dialysis immediately post-heart transplantation. Predictors included longer ischemic time, serum creatinine at transplantation >1.2 mg/dL, prior cardiac surgery, higher recipient body mass index, support of mechanical ventilation or extracorporeal membrane oxygenation, and history of congenital heart disease or restrictive/hypertrophic cardiomyopathy ( $p < 0.05$ ). Patients on posttransplant dialysis had a higher risk of all-cause mortality, 30-day mortality and 1-year mortality ( $p < 0.001$ ).

Youn JC, et al. (2022). Post-transplantation outcomes of sensitized patients receiving durable mechanical circulatory support. *J Heart Lung Transplant*, 41(3):365-372. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34895990/>

- Single-center, prospective, observational study compared sensitized-mechanical circulatory support (MCS) patients with sensitized non-MCS patients, non-sensitized MCS patients, and non-sensitized non-MCS patients. The study showed that sensitized MCS patients had significantly lower rates of antibody-mediated rejection (AMR) and an earlier decline in panel-reactive antibody (PRA) levels than sensitized non-MCS patients. Sensitized MCS patients showed comparable rates of primary graft dysfunction, 1-year survival, and 1-year freedom from AMR with non-sensitized MCS patients and non-sensitized non-MCS patients.

Han J, et al. (2022). Impact of using higher-risk donor hearts for candidates with pre-transplant mechanical circulatory support. *The Journal of Heart and Lung Transplantation*. 2022;41(2):237-243. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34815161/>

- Retrospective analysis using the UNOS database evaluated post-heart transplant (HTx) outcomes after use of higher-risk donor hearts for candidates supported with pre-HTx mechanical circulatory support (MCS). Patients supported with pre-transplant ECMO, surgical BiVAD, or IABP who received higher-risk donor hearts had 1 year survival comparable to recipients of

standard criteria donor hearts. However, stable patients on continuous flow LVAD support had increased mortality compared to those who received standard-risk donor hearts ( $p = 0.004$ ).

Hirji SA, et al. (2022). Contemporary nationwide heart transplantation and left ventricular assist device outcomes in patients with histories of bariatric surgery. *Journal of Cardiac Failure*. 2022;28(2):330-333. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34509598/>

- The retrospective analysis evaluating the cumulative in-hospital mortality rate in the HT cohort was < 6%. The incidence of bleeding requiring transfusion, acute kidney injury, vascular complications, and rejection were 19.1%, 76.2%, 76%, and 14.3%, respectively. These risk-adjusted hospital outcomes were not significantly different from those of obese patients without previous bariatric surgery.

Zhou L, et al. (2022). Noninvasive methods to reduce cardiac complications postheart transplant. *Current Opinion in Organ Transplantation*. 2022;27(1):45-51. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34907978/>

- The review article summarized newer noninvasive screening techniques for the detection of clinically significant rejection and potential new biomarkers and therapies in preventing allograft vasculopathy

Vest AR, et al. (2022). New-onset diabetes mellitus after adult heart transplantation and the risk of renal dysfunction or mortality. *Transplantation*, 106(1):178-187. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33496556/>

- Retrospective analysis using ISHLT Thoracic Organ Transplant Registry. Among 26,263 eligible subjects, 21% had new-onset post-HT DM within 5 years of HT. Post-HT DM was associated with increased risk of severe renal dysfunction and death or retransplantation compared to patients without post-HT DM.

Black RJ, et al. (2021). Swallowing and laryngeal complications in lung and heart transplantation: Etiologies and diagnosis. *J Heart Lung Transplant*, 40(12):1483-1494. Retrieved from: <https://doi.org/10.1016/j.healun.2021.08.006>

- Review article that discusses how oropharyngeal dysphagia and dysphonia may occur after heart and lung transplants and how swallowing and laryngeal dysfunction may impact patient care in order to improve patient outcomes after transplant.
- This article speculates that intubation, ICU-acquired muscle weakness, gastric motility disorders, and medications or situations that influence neurological function (e.g., ICU delirium, sedating medications, etc.) may be the reason why patients who receive heart or lung transplants may experience swallowing or laryngeal complications after transplant.
- These complications differ in their time to resolution, ranging from resolving before discharge after the transplant up to around 200 days depending on the type of laryngeal or oropharyngeal issue arises. Management also varies depending on the exact complication and severity, but all can impact patient morbidity, increase hospital stays, and increase healthcare costs.

Jeon J, et al. (2021). Prognostic factors of renal outcomes after heart transplantation: A nationwide retrospective study. *J Clin Med*, 10(21):5110. Retrieved from: <https://doi.org/10.3390/jcm10215110>

- Multicenter retrospective cohort study in South Korea from January 2008 to September 2016. Of the 736 patients who received a heart transplant during the study period, half had three or more comorbidities, the most common being hypertension, chronic pulmonary disease, and diabetes. Out of the 736 patients included in the study, 27.8% required perioperative renal replacement therapy (RRT) during their admission for heart transplant.

- Of the 654 patients who survived discharge, 12 people (1.8%) developed end-stage kidney disease (ESKD). Perioperative RRT > 21 days, use of inotropes/vasopressors, and no use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB) all were significantly associated with the development of ESKD ( $p < 0.001$ ,  $p < 0.002$ , and  $p < 0.001$ , respectively).
- Of the 654 patients who received follow-up, 561 did not have pre-existing CKD. Of those, 104 patients (18.5%) were newly diagnosed with CKD after transplant. Older age, ECMO, and RRT were all associated with an increased risk of developing new CKD ( $p < 0.01$ ,  $p < 0.01$ , and HR > 21 days 3.69, respectively).
- Mortality was associated with pre-existing renal disease (15.0% survival vs. 28.1% death,  $p = 0.01$ ), more mechanical ventilation (24.6% vs. 86.0%,  $p < 0.001$ ), use of ECMO (21.6% vs. 61.4%,  $p < 0.001$ ), more RRT (22.5% vs. 91.8%,  $p < 0.001$ ), and less use of ACEi/ARB (32.3% vs. 15.8%,  $p = 0.01$ ).

Venema CS, et al. (2021). Post-transplant inotrope score is associated with clinical outcomes after adult heart transplantation. *Clin Transplant*, 35(8):e14347. Retrieved from: <https://doi.org/10.1111/ctr.14347>

- Single center retrospective study performed in the Netherlands from January 2007 to June 2020 to determine if inotrope use impacted post-transplant outcomes. The population was divided into three different cohorts based on their inotrope score (higher inotrope score = higher use of inotropes). Tertile one had inotrope score of 2.1 to 12.4, tertile two had inotrope score of 12.5 to 24.4, and tertile three had inotrope score of 24.5 to 75.6. All tertiles measure inotrope use within the first 48 hours after transplant.
- Cardiac index, pulmonary artery pressures, and central venous pressures were not significantly different between the three groups. Arterial blood pressures were significantly different in the second and third tertiles compared to the first. The number of patients requiring extracorporeal life support (ECLS) was higher in the third tertile compared to the first and second (29.6% vs. 11.1% vs. 3.7%, respectively). Patients in the third tertile had a lower risk of needing CVVH than patients in the second and third tertiles (11% vs. 41% vs. 78%,  $p = 0.04$  between the first and second tertiles and  $p < 0.01$  between the first and third tertiles). Mortality at 30-days, 1-year, and 5-years were not significantly different between the three groups. However, ICU length of stay was significantly shorter between the first and second tertiles (4.0 days vs. 8.5 days,  $p < 0.01$ ) and between the first and third tertiles (4.0 days vs. 14.0 days,  $p < 0.01$ ).

Duerinckx N, et al. (2021). Depressive symptoms at 1 year after surgery increase the risk of cardiac allograft vasculopathy and mortality in heart transplant recipients: A prospective cohort study. *Gen Hosp Psychiatry*, 71:20-26. Retrieved from: <https://doi.org/10.1016/j.genhosppsy.2021.03.008>

- Single center prospective cohort study performed in Belgium from January 2000 to August 2014. The study's aim was to determine if post-transplant outcomes of cardiac allograft vasculopathy (CAV) and mortality are related to depression at 1-year after heart transplant.
- Of the study population, 23.7% had depressive symptoms (17.9% mild, 4.7% moderate, 1.1% severe). In one of the study analyses, depressive symptoms resulted in an increased mortality risk ( $p = 0.003$ ). Unadjusted and adjusted analysis results showed significantly increased mortality in the group with depressive symptoms (unadjusted:  $p = 0.004$ ; adjusted:  $p = 0.002$ ). For every 6-point increase in the BDI scale (scale to quantify depressive symptoms), there was a 31% increase in mortality. The study also showed that depressive symptoms increased the risk for CAV ( $p = 0.026$ ).

Roest S, et al. (2021). Influence of renal insufficiency pre-heart transplantation on malignancy risk post-heart transplantation. *ESC Heart Fail*, 8(3):2172-2182. Retrieved from: <https://doi.org/10.1002/ehf2.13309>

- Single center retrospective cohort study performed in the Netherlands from January 1, 2000 to October 31, 2017. The aim of this study was to determine if the duration of heart failure and CKD pre-transplant impact the risk of malignancy post-transplant.
- There was no significant difference in duration of HF between the malignancy group and no-malignancy group ( $p = 0.44$ ). Patients with malignancy were more likely to develop CKD post-transplant compared to those without malignancy (78% vs. 62%,  $p = 0.017$ ). Cumulative incidence of malignancies was 11.8% at 5-years, 28.4% at 10-years, and 40.3% at 15-years. The study's analysis found that age of HF outset ( $p < 0.001$ ), pre-transplant CKD ( $p = 0.015$ ), development of a primary EBV infection post-transplant ( $p = 0.039$ ), and the number of immunosuppressive drugs 1-year post transplant ( $p = 0.04$ ) all significantly increased the risk of malignancy. CKD pre- (61% vs. 39%,  $p = 0.026$ ) and post-transplant (86% vs. 63%,  $p = 0.017$ ) were more prevalent in patients with solid organ malignancies. 37% of patients with malignancies died by the end of the study period compared to 21% of the patients without malignancies ( $p = 0.015$ ).

Nair N, et al. (2021 Mar). Risk prediction model for cutaneous squamous cell carcinoma in adult cardiac allograft recipients. *World J Transplant*, 11(3):54-69. Retrieved from: <https://doi.org/10.5500/wjt.v11.i3.54>

- Multicenter retrospective cohort study performed using the UNOS registry from 2000 to 2015. The study's aim was to predict the incidence of cutaneous squamous cell carcinoma (cSCC) and identify any risk factors after heart transplant.
- 7.70% of the study population developed cSCC. There were 10 variables associated with increased risk for cSCC, including age (older age), sex (male gender), race (white), HLA mismatch level (lower mismatch level), PRA against both Class I and II antigens (lower PRA levels), CAD or congenital heart disease, malignancy status at listing, malignancy status at transplant, and OKT3 induction. The study showed that patients with cSCC had a 1.51-fold higher mortality risk compared to the non-cSCC group.

Barghash MH, et al. (2020). Recombinant herpes zoster vaccine after heart transplantation: A single-center experience. *J Heart Lung Transplant*, 39(12):1501-1503. Retrieved from: <https://doi.org/10.1016/j.healun.2020.09.001>

- Single center retrospective cohort study performed in the United States from September 2018 to July 2019. The aim of this study was to assess the clinical safety and efficacy of the Shingrix vaccine after transplant.
- All 65 patients included in the study had a prior varicella infection shown by positive antibody titers. 70.8 % of patients received both doses of Shingrix. Adverse effects occurred in 35% of the patients after the first Shingrix vaccine, and 28% experienced adverse effects after the second Shingrix vaccine. There were no episodes of rejection after Shingrix vaccination. 1 patient developed a herpes zoster infection 2 months after the first dose of Shingrix.

Rolid K, et al. (2020). Long-term effects of high-intensity training vs moderate intensity training in heart transplant recipients: A 3-year follow-up study of the randomized-controlled HITS study. *Am J Transplant*, 20(12):3538-3549. Retrieved from: <https://doi.org/10.1111/ajt.16087>

- Randomized prospective cohort study in Norway for a 3-year follow up after heart transplant. The aim of this study was to determine if high-intensity interval training (HIT) or moderate intensity continuous training (MICT) better impacted peak oxygen consumption ( $VO_{2peak}$ ) after heart transplant. 62 patients completed the follow-up tests.
- While both groups showed an increase in  $VO_{2peak}$ , the HIT arm showed a larger increase compared to the MICT group at 1 year follow-up. At the 3-year follow-up, there was no significant

difference between the two groups with regard to  $VO_{2peak}$ . The study did show that the aerobic threshold increased significantly higher in the HIT group compared to the MICT group at the 3 year follow-up when compared to baseline ( $p = 0.024$ ). Patients appeared to have difficulty continuing HIT long-term.

Wang TJ, et al. (2020). Long-term outcomes and risk factors of renal failure requiring dialysis after heart transplantation: A nationwide cohort. *J Clin Med*, 9(8):2455. Retrieved from:

<https://doi.org/10.3390/jcm9082455>

- Multicenter retrospective cohort study performed in Taiwan from 1997 to 2009. The aim of this study was to evaluate renal failure after heart transplant to determine the incidence, the association with long-term mortality, and the risk factors associated.
- 28.4% of patients in the study population developed renal failure requiring dialysis. Significant differences between the dialysis and non-dialysis groups were gender (males more common in dialysis group, 79.4% vs. 66.5%,  $p < 0.001$ ), HBV carrier status, cirrhosis, DM, CKD, HTN, primary diagnosis for HT, and immunosuppressant usage ( $p < 0.05$ ).
- One-year, three-year, and five-year mortality rates from any cause were all higher in the dialysis group compared to the non-dialysis group. Mortality in the dialysis group was higher in the first year after transplant and decreased as time passed.
- 21% of the study population required early dialysis (during the initial hospitalization where transplant was performed), and 7.4% of the study population required late dialysis (during subsequent hospitalizations after the transplant). While mortality in both the early and late dialysis groups was higher than in the non-dialysis group, the mortality between the two dialysis groups was not significant.
- The study analysis found that risk factors for renal failure requiring dialysis after heart transplant included HBV infection, pre-transplant diagnosis of diabetes, pre-existing CKD, history of AKI, and a primary heart transplant diagnosis of CAD. Factors that may be associated with an increased risk of early dialysis included CKD and a primary diagnosis of CAD. Factors that may be associated with an increased risk of late dialysis included a prescription of sirolimus, mycophenolate mofetil, or azathioprine.

Punnoose LR, et al. (2020). Pregnancy outcomes in heart transplant recipients. *J Heart Lung Transplant* [Epub ahead of print.] Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/32201090>

- Livebirths occurred in 69% of 157 reported pregnancies in 91 patients, and there were no neonatal deaths.
- The most common complications during pregnancy were preeclampsia (23%) and infections (14%). Rejection occurred during pregnancy in 9% and within 3 months postpartum in 7% of patients. Miscarriages occurred at a rate of 26%; 49% of patients who miscarried had mycophenolic acid exposure.

Alvarez-Alvarez RJ, Barge-Caballero E, Chavez-Leal SA, et al. (2015) Venous thromboembolism in heart transplant recipients: incidence, recurrence and predisposing factors. *J Heart Lung Transplant*. 2015 Feb;34(2):167-74. doi:10.1016/j.healun.2014.09.039. Epub 2014 Oct 2. Retrieved at:

<https://pubmed.ncbi.nlm.nih.gov/25434523/>

- VTE is a frequent complication after HT, mainly during the first post-operative year. In view of a high recurrence rate, long-term anti-coagulation should be considered in HT recipients who experience a first VTE episode.

Wang YJ, et al. (2016.) Malignancy after heart transplantation under everolimus versus mycophenolate mofetil immunosuppression. *Transplant Proc*, 48(3):969-73. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/27234781/>

- EVR treatment after heart transplant is associated with a lower risk of malignancy than is MMF treatment. The 2-year survival rate after malignancy was similar between EVR and MMF groups.

Ciarka A, et al. (2016). Effect of heart rate and use of beta blockers on mortality after heart transplantation. *Am J Cardiol*, 118(12):1916-1921. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/27743576/>

- In a large single-center cohort of HT recipients, higher heart rate and nonuse of  $\beta$  blockers were independently associated with higher mortality.

Jahangirifard A, et al. (2017) The effect of desmopressin on the amount of bleeding and transfusion requirements in patients undergoing heart transplant surgery. *Basic Clin Pharmacol Toxicol*, 121(3):175-80. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28326680>

- Desmopressin may reduce postoperative bleeding in patients undergoing heart transplant surgery. Further studies are required to confirm the potential effect of desmopressin on establishing hemostasis following heart transplantation.

Fahrleitner-Pammer A, et al. (2017). Teriparatide treatment in a heart transplant patient with a chronic kidney disease and a low-turnover bone disease: a case report. *Osteoporos Int*, 28(3):1149-1152. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27988794>

- Low-turnover bone disease is a complication of chronic kidney disease and a long-term steroid therapy. Currently, the only bone anabolic treatment available is teriparatide (TPTD). So far, no data exist in heart transplant patients, and only one single case with histomorphometric analysis of a dialysis patient with a low-turnover bone disease has been published. The current report shows the effect of a 1-year TPTD therapy in a cardiac transplant patient with 10 vertebral and 3 peripheral fractures who had developed a chronic kidney failure while receiving triple immunosuppressive therapy. A transiliac bone biopsy following tetracycline labeling was performed prior and after 1 year of treatment, showing an increase in the bone formation and improvement of the structural indices (20-fold increase of osteoid volume/bone volume, fourfold increase of osteoid surface/bone surface and increases of wall thickness (+15%), trabecular thickness (+9%), and trabecular number (+38%)). Bone mineral density was stable, no new vertebral fractures had occurred, the therapy was well-tolerated, and the patient improved clinically.

Bennett AL, (2017). Hypertension in patients with cardiac transplantation. *Med Clin North Am*, 101(1):53-64. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27884235>

- Hypertension affects more than 95% of patients. Increased blood pressure poses a significant cardiovascular morbidity and mortality in these patients; it should be identified quickly and needs to be managed appropriately. Understanding the pathophysiology and contributing factors to this disease in these complex and unique patients is the key to appropriate treatment selection

## 5.10 Miscellaneous Review Articles

Villegas-Galaviz J, et al. Clinical outcomes of heart transplantation using hepatitis c-viremic donors: A systematic review with meta-analysis. *J Heart Lung Transplant*, S1053-2498(22)00015-8. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35153130/>

- A systematic review with meta-analysis that evaluated outcomes of heart transplantation from hepatitis C virus (HCV)-viremic donors to nonviremic recipients. The HCV-transmission rate was >97%, but the cure rate was 100% with direct-acting antiviral (DAA) therapy. The 6 and 12-month survival were 95.6% and 92.9% respectively with no deaths associated with HCV infection.

Coniglio AC, et al. (2021). Innovations in heart transplant: A review. *J Card Fail*, S1071-9164(21):00437-1. Retrieved from: <https://doi.org/10.1016/j.transproceed.2021.08.048>

- Mainly discusses expansion in the donor pool by the addition of donation after cardiac death (DCD) donors and hepatitis C positive donors, as well as how donor-recipient matching and post-transplant care have improved outcomes.

Guerrero-Miranda CY and Hall SA. (2021). Rethinking the future with evolving technology: It's time to empower change in heart transplantation. *Am J Transplant*, 21(2):453-455. Retrieved from: <https://doi.org/10.1111/ajt.16221>

- Review article discussing how biomarkers may be used to identify patients at higher risk for events like rejection after heart transplantation.

Loungani RS, et al. (2020). Biomarkers in advanced heart failure: Implications for managing patients with mechanical circulatory support and cardiac transplantation. *Circ Heart Fail*, 13(7):e006840. Retrieved from: <https://doi.org/10.1161/circheartfailure.119.006840>

- Review article discussing traditional and newer biomarkers in both patients with LVADs and patients receiving a heart transplant. It discusses how these biomarkers may be used in clinical practice to improve patient care and outcomes.

Andrew J, Macdonald P. (2015) Latest developments in heart transplantation: a review. *Clin Ther*. 2015 Oct 1;37(10):2234-41. doi: 10.1016/j.clinthera.2015.08.019. Retrieved at: <https://www.ncbi.nlm.nih.gov/pubmed/26497799>

- A review of recently published literature in heart transplant

