Greek - International Experience

End-Stage Heart Failure

Heart Transplantation

Mechanical Circulatory Support

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Heart transplantation is currently the most accepted treatment for end-stage HF.

Although controlled trials have never been and will probably never be conducted, there is consensus that transplantation, provided proper selection and listing criteria are applied, significantly improves survival, functional capacity and quality of life associated with increase in return to usual daily activities (including work), compared with conventional pharmacological and non-pharmacological treatment.
Incremental Improvement of Crude (unadjusted) Survival in the Most Recent Era
Ελλάδα: Επιβίωση μετά Μεταμόσχευση Καρδιάς

Comparing with ISHLT

<table>
<thead>
<tr>
<th>Time</th>
<th>OCC</th>
<th>Europe</th>
<th>ISHLT Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>89,3%</td>
<td>81,1%</td>
<td>86,3%</td>
</tr>
<tr>
<td>3 years</td>
<td>86,2%</td>
<td>76,1%</td>
<td>80,1%</td>
</tr>
</tbody>
</table>
## Indications and Contraindications

**ESC/HFA Guidelines 2016**

<table>
<thead>
<tr>
<th>Patients to consider</th>
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<tbody>
<tr>
<td>- End-stage HF with severe symptoms, a poor prognosis and no remaining alternative treatment options</td>
</tr>
<tr>
<td>- Motivated, well informed and emotionally stable</td>
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<tr>
<td>- Capable of complying with the intensive treatment required postoperatively</td>
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<table>
<thead>
<tr>
<th>Contraindications</th>
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</thead>
<tbody>
<tr>
<td>- Active infection</td>
</tr>
<tr>
<td>- Severe peripheral arterial or cerebrovascular disease</td>
</tr>
<tr>
<td>- Current alcohol or drug abuse</td>
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<tr>
<td>- Treated cancer in previous 5 years</td>
</tr>
<tr>
<td>- Unhealed peptic ulcer</td>
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<tr>
<td>- Recent thromboembolism</td>
</tr>
<tr>
<td>- Significant renal failure <em>(e.g. creatinine clearance &lt; 30 mL/min)</em></td>
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<tr>
<td>- Significant liver disease</td>
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<tr>
<td>- Systemic disease with multiorgan involvement</td>
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<tr>
<td>- Other serious co-morbidity with poor prognosis</td>
</tr>
<tr>
<td>- Emotional instability or untreated mental illness</td>
</tr>
<tr>
<td>- High, fixed pulmonary vascular resistance (&gt;3-4 Wood Units)</td>
</tr>
</tbody>
</table>
Hypothesis: With each hospitalization, there is myocardial and/or renal damage leading to further progression of the disease.

Risk of death increases substantially with each subsequent HF hospitalization.

Setoguchi S et al. Am Heart J 2007

HF hospitalization: a. independent predictor of poor outcome; b. major contributor
Key Evidence 1 - Peak Oxygen Uptake

In the presence of a beta-blocker, a cutoff for peak VO2 of ≤12 ml/kg/min and achievement of an anaerobic threshold (RER > 1.05) on optimal pharmacological and non-pharmacological therapy should be used to guide listing (Class I, Level of Evidence B).

Especially in young patients (≤50 years) and women or in patients not reaching true peak VO2, it is reasonable to consider using alternate standards in conjunction with peak VO2 to guide listing, including percent of predicted (≤50%) peak VO2 and/or VE/VCO2 slope of >35, which can be measured throughout the entire exercise duration and which, according to some investigators, is of greater prognostic value than a peak VO2 of <14 ml/kg/min (Class IIa, Level of Evidence B).

MR Mehra et al, J Heart Lung Transplantation 2016, January
Pulmonary artery hypertension and elevated PVR should be considered as relative contraindications to cardiac transplantation when the PVR is >3-4 Woods units or the PVR index is >6 or the TPG (mean transpulmonary gradient) exceeds >15mmHg, given that if the PAS exceeds 60 mmHg in conjunction with any of the aforementioned 3 variables the risk of right heart failure and early death is increased (Class I, Level of Evidence C).

A vasodilator challenge should be attempted when the pulmonary artery systolic pressure is ≥50mmHg and either TPG is ≥15 or PVR is >3Wood units while maintaining a systolic arterial blood pressure >85 mm Hg to assess the reversibility of high PVR.

Serial right heart catheterization should be performed more frequently in patients with marginal initial reductions in the PVR despite aggressive therapy (e.g., VAD and high-dose inotropes) to determine their ongoing acceptability for cardiac transplantation.
Historical Perspective of Heart Transplantation

major landmarks of transplantation associated with progressive improvement in survival

1960. Surgical technique of heart transplantation pioneered by Normand Shumway
1967. Christiaan Barnard performs the first human to human heart transplantation
1969. Denten Cooley uses first total artificial heart as a bridge to transplant
1973. Philip Caves develops technique of endomyocardial biopsy. Margaret Billingham develops a system for reading specimens
1980. Cyclosporine approved by the FDA
1984. First successful use of a ventricular assist device
1991. Sievers develops the bicaval technique for orthotopic heart transplantation
1990's. Introduction of MMF and tacrolimus
Late 1990's. Trials with sirolimus and everolimus. Introduced clinically early 2000 (everolimus not yet FDA approved in the USA)

SA Hunt, J Am Coll Cardiol 2008, August
MicroRNAs as Non-Invasive Biomarkers of Heart Transplant Rejection

4 circulating miRNAs identified allograft rejection

Circulating microRNAs identify ongoing heart allograft rejection and may spare 70-80% of endomyocardial biopsies

Duong Van Huyen JP et al, Eur Heart J 2014, Aug 31
Maintenance Immunosuppression Drug Combinations at 1 Year and at 5 Years after Adult Heart Transplant, for the Same Patients at 1 and 5 Years

(Follow-Up: January 2004–June 2015)
Have Risk Factors for Mortality after Heart Transplantation Changed over Time? Insights from 19 Years of Cardiac Transplant Research Database Study

Acceptable values for immunosuppressant levels should be adjusted as a function of age, with more aggressive immunosuppression in younger patients and reduced immunosuppression in older recipients.

JA Tallaj et al, J Heart & Lung Transpl 2014, December
Percentage of Adult Heart Transplant Recipients Experiencing Treated Rejection between Transplant Discharge and 1-Year Follow-Up by Era

Ελλάδα

1ος χρόνος: 15-20% των μεταμοσχευμένων εισάγονται με απόρριψη

Treated rejection = Recipient was reported to (1) have at least one acute rejection episode that was treated with an anti-rejection agent; or (2) have been hospitalized for rejection.

LH Lund: The Registry of the ISHLT
Thirty-Third Official Adult Heart Transplantation Report—2016
The Journal of Heart & Lung Transplantation, October 2016
Freedom from Cardiac Allograft Vasculopathy and Malignancy by Recipient Age and Immunosuppression

The Registry of the International Society for Heart and Lung Tx
Thirtieth Official Report - October 2013

CAV

Malignancy

No pair-wise comparisons were significant at p < 0.05

All pair-wise comparisons were significant at p < 0.0001 except 60-69 vs. 70+ (p=0.9554)
Causes of Death by Duration Post-Transplant
(deaths: January 2009-June 2014)
Πρώιμη Δυσλειτουργία Μοσχεύματος (Graft Failure)

Ζωνιαία Ισχαιμία

Ανοσολογική Αντίδραση
VA-ECMO and Cardiogenic Shock
Όψιμη Δυσλειτουργία Μοσχεύματος (Graft Failure)
Όψη δυσλειτουργία μοσχεύματος (Graft Failure)

Κυτταρική Απόρριψη

Χημική Απόρριψη (C4D staining)
Mortality on waiting list for HT

1st Year  49-69%
2nd Year  81-89%

The Journal of Heart & Lung Transplantation, October 2017
Current Estimate of the Number of Advanced HF Patients

Leslie W Miller, Maya Guglin: JACC 2013

45-50% Preserved Systolic Function 3.0-3.5 M

300 Million US Population

HF = 2.6% Population* or 7 Million Total

50-55% Systolic HF 3.0-3.5 Million

Class III B 100-150,000

Class IV 75-150,000

Theoretical Candidates for Mech Circ Support

Class III B+IV < 75 yrs

150-250,000 Pts
Seventh INTERMACS Annual Report: Risk Factor Analysis from more than 15,000 Mechanical Circulatory Support Patients

JK Kirklin et al, The Journal of Heart & Lung Transplantation 2015, December
Ventricular Assist Devices for Treatment of Acute Heart Failure and Chronic Heart Failure

HeartMate II axial flow device

HVAD centrifugal flow device

The two LVAD systems that have received CE Mark and FDA approval

JN Kirkpatrick et al, Heart 2015, May 6
Ελλάδα: >60% των μεταμοσχευομένων υποστηρίζονται μηχανικά.
Destination Therapy is Growing and Accounts for more than 40% of Implants

JK Kirklin et al, J Heart & Lung Transplantation 2014, June
Kaplan-Meier Survival Curves, Stratified by Device Strategy and Era

JK Kirklin et al, JHLT 2017, October

Intermacs Continuous Flow LVAD/BiVAD Implants: 2008 – 2016, n=17633

Bridge to Transplant Listed and Destination Therapy by Era (n=12150)

<table>
<thead>
<tr>
<th>Device Strategy</th>
<th>% Survival post implant</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At implant n</td>
<td>deaths</td>
<td>1 yr</td>
<td>2 yrs</td>
</tr>
<tr>
<td>BTT (2008-2012)</td>
<td>1922 484</td>
<td></td>
<td>85%</td>
<td>76%</td>
</tr>
<tr>
<td>BTT (2013-2016)</td>
<td>2839 470</td>
<td></td>
<td>85%</td>
<td>77%</td>
</tr>
<tr>
<td>DT (2008-2012)</td>
<td>2317 1364</td>
<td></td>
<td>75%</td>
<td>62%</td>
</tr>
<tr>
<td>DT (2013-2016)</td>
<td>5072 1511</td>
<td></td>
<td>78%</td>
<td>66%</td>
</tr>
</tbody>
</table>

P(overall) < .0001
P(BTT v DT) 2008-2012 < .0001
P(BTT v DT) 2013-2016 < .0001

Event: Death (censored at transplant and device cessation)
Kaplan-Meier Survival Curves, Stratified by Era and Biventricular Support (CFBiVAD) vs Total Artificial Heart (TAH)

JK Kirklin, JHLT 2017, October

Intermaccs

Implants: June 2006 – December 2016
CFBiVADs vs. TAH, n=991

<table>
<thead>
<tr>
<th>Pump</th>
<th>n</th>
<th>deaths</th>
<th>1 yr</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFBiVAD (2006-2012)</td>
<td>231</td>
<td>133</td>
<td>56%</td>
<td>49%</td>
</tr>
<tr>
<td>CFBiVAD (2013-2016)</td>
<td>387</td>
<td>171</td>
<td>55%</td>
<td>47%</td>
</tr>
<tr>
<td>TAH (2006-2012)</td>
<td>147</td>
<td>37</td>
<td>59%</td>
<td>44%</td>
</tr>
<tr>
<td>TAH (2013-2016)</td>
<td>226</td>
<td>93</td>
<td>52%</td>
<td>37%</td>
</tr>
</tbody>
</table>

P(overall) = .03
P(CFBivad vs. TAH) 2013-2016 = .77
P(CFBiVAD vs.TAH) 2008-2012 = .04

Event: Death (censored at transplant and device cessation)

Months post implant
RV Dysfunction is One of the Major Determinants of in-Hospital Mortality

✓ Evaluation of right ventricular function is crucial as postoperative right ventricular failure greatly increases perioperative mortality and reduces survival to, and after, transplantation. Consequently, BiVAD, rather than LVAD, support should be considered for BTT in patients with biventricular failure or at high risk of developing RV failure after LVAD implantation.

Reduced RV free wall peak longitudinal strain was associated with an increased risk for RV failure.

Vasopressor requirement, SGPT, bilirubin, creatinine
Results

Univariate analysis:
• High RAP (p=0.001)
• High systolic PAP (p=0.001)
• Low PAPi (p<0.001)
• High RA/PCWP (p<0.001)
• Low systolic BP and low SVR (p=0.002)

Multivariate analysis:
• PAPi (OR 0.88; 95% CI 0.79-0.98)
• RA/PCWP (OR 1.78; 95% CI 0.90-3.51)

PAPI \leq 2.8 and RA/PCWP > 0.53 \rightarrow RHF
PAPI \leq 2.8 and RA/PCWP > 0.53 \rightarrow Poor survival
RV Functional Improvement with 2 weeks IABP

**Before IABP**
- RA = 13 mmHg
- mPA = 55 mmHg
- W = 43 mmHg
- RV strain = -13%

**Post IABP**
- RA = 7 mmHg
- mPA = 36 mmHg
- W = 28 mmHg
- RV strain = -17%
Patients with > 2 months of severe symptoms despite optimal medical and device (CRT/ICD) therapy AND MORE THAN ONE of the following:

- LVEF < 25% and, if measured, peak VO2 < 12 mL/kg/min
- ≥ 3 HF hospitalizations in previous 12 months without an obvious precipitating cause
- Dependence on IV inotropic support
- Progressive end organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥ 20 mm Hg and SBP ≤ 80–90 mmHg or CI ≤ 2 L/min/m²)
- Deteriorating right ventricular function

ESC/HFA Guidelines 2012, 2016

Patients Potentially Eligible for Implantation of a Ventricular Assist Device

REVIVE-IT Trial... the earlier the better?
Unexpected Abrupt Increase in Left Ventricular Assist Device Thrombosis

Recommendations for LVAD therapy should account for this updated risk-benefit profile.

Eighth Annual INTERMACS Report: Special Focus on Framing the Impact of Adverse Events

* Major Event: First occurrence of infection, bleeding, device malfunction, stroke or death

- Profiles 4-7, n=1684
  Events=1257

- Profiles 2 & 3: n=7593
  Events=5403

- Profile 1: n=1660
  Events=1225

P(overall) < .0001

JK Kirklin, JHLT 2017, October
LVAD - Επιπλοκές

Follow-up 2 ετών

❖ Αιμορραγία πεπτικού → 20-30%
❖ Αιμορραγικό ΑΕΕ → 5-11%
❖ Ισχαιμικό ΑΕΕ → 8-10%
❖ Θρόμβωση συσκευής → 4-8%
❖ Λοιμώξεις → 30-50%
❖ Ανεπάρκεια Δεξιάς Κοιλίας → 11%
❖ Ευαισθητοποίηση έναντι δυνητικού δότη
Εντός 2 ετών, 30% των ασθενών που έλαβαν LVAD σαν BTT, τελικά μεταπίπτουν σε DT
Morbidity and Mortality in Heart Transplant Candidates Supported with Mechanical Circulatory Support. Is Reappraisal of the Current UNOS Thoracic Organ Allocation Policy Justified?

O Wever-Pinzon et al, Circulation 2013, January 29

28% of LVAD-supported patients in the current era are listed in status 1A because of a device-related complication.
When the Failing, End-Stage Heart Is Not End-Stage

Left Ventricular Assist Device and Drug Therapy for the Reversal of Heart Failure

Physical Training in End-Stage HF Patients with VAD Implantation Up-Regulates Physiological Growth Signaling Pathways

✓ up-regulation of pro-hypertrophic Akt
✓ suppression of anti-hypertrophic JNK

BTT-LVAD is estimated to offer >3.8 additional life-years for patients waiting ≥6 months.
A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure (MOMENTUM 3)

Survival Free of Disabling Stroke or Reoperation to Replace or to Remove the Pump

HeartMate III

The organ donation crisis in Greece does not exclusively represent direct negative effects of the financial crisis, but reflects the underlying inadequacy of the health system and people’s attitude towards organ donation.
Σύνολο μεταμοσχεύσεων καρδιάς: 152
HTx σε ασθενείς με VADs: 72
Εξ αυτών BiVADs: 46

Heart Transplant Progress at the OCSC before and after the Initiation of the Mechanical Circulatory Support Programme

Συμβόλωση ΜΤΧ Καρδιάς
ΜΤΧ Καρδιάς από VADs
Algorithm for Selection of LVAD Candidates

- Advanced HF
  - EF<25%
  - Optimal medical management
  - CRT if QRS>120 msec
- NYHA III-IV
- Six minute walk <300 m
- Peak VO2<14 mL/kg/min
- Frequent hospital admissions

Heart transplant/LVAD Evaluation

- Eligible for transplant, donor available
  - Heart Transplant
- Eligible for transplant, donor not available
  - LVAD as a bridge to transplant

Not eligible for transplant
- Too old
- High BMI
- High PVR
- Recent malignancy
- HIV
- Renal insufficiency
- Hepatic insufficiency

Consider LVAD