The promise of a healthy heart.

VAD or heart transplantation after age 65

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Disclosure Slide

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- **Consulting fees**: n/a

- **Speaker fees**: n/a

- I will NOT discuss off-label uses of drugs
Objectives

- Review the evidence for advanced HF therapies in older patients
- Outcomes with heart transplant in the older population
- Outcomes with LVAD
- Heart transplant versus LVAD
Age-adjusted leading cause of death, US 2009

Figure 6. Age-adjusted death rates for selected leading causes of death: United States, 1950–2008

National Vital Statistics Reports 2011
THE STATE OF THE HEART IN CANADA

1 MILLION
CANADIANS ARE LIVING WITH HEART FAILURE.

100,000+
Canadians are hospitalized annually due to heart failure – the most common reason for hospital admission.

2.1 YEARS
the median survival rate for heart failure patients.

40 TO 50%
of people with congestive heart failure die within five years of diagnosis.

1.4 MILLION
HOSPITAL STAYS PER YEAR

UP TO
$3 B
annual cost for managing moderate and severe heart failure patients in Canada.

1 in 5
Canadians over the age of 40 have a risk of developing heart failure.

10 DAYS
the average length of stay for heart failure patients.

26.4 DAYS
of hospital resources used by the average patient in their first year of treatment.

Naylor et al, ICES 1999
Senni et al, Circ 1998
Lee et al, Circulation 2009
Costanzo MR et al, AHJ 2008
Heidenreich PA et al, Circulation. 2011
Courtesy of Dr. HJ Ross.

The promise of a healthy heart.
~ 200 transplants
75 VADs

50,000 Advanced HF

500,000 with HF diagnosis

Advanced therapies
Experimental Rx
Cardiac replacement

Tailored therapy
IV Vasodilators
IV diuretics

Optimization of oral therapy
Referral for CRT/ICD

Aldosterone antagonist
ACEi/ARB, Beta blocker
Diet, exercise prescription
Risk factor control

Chronic Disease Management

The promise of a healthy heart.
Over the next 20 years:
• Prevalence will increase by 25%
• Annual direct medical costs will increase $77.7 billion (2008 dollars)
Prognostic Markers

- **General**
  - Age, diabetes, sex, weight (BMI), etiology of HF, comorbidities (COPD, cirrhosis)

- **Laboratory markers**
  - Na, creatinine (and eGFR), urea, BUN,
  - Hgb, % lymphocytes,
  - uric acid
  - Low HDL
  - Insulin resistance

- **Urine**
  - Abluminuria
  - NGAL - neutrophil gelatinase associated lipocalin

- **Biomarkers**
  - BNP, NT pro BNP, troponin, CRP, cystatin C, GDF-15 (growth differentiation factor), serum cortisol, TNF, ET, NE, midregional-pro-adrenomedullin (MR-proADM), pro-apoptotic protein apoptosis-stimulating fragment (FAS)

- **Medication**
  - Intolerance to ACEI, diuretic dose
  - FC IV
    - Especially if sustained > 90 days
    - 6 minute walk

- **Cardiopulmonary markers**
  - Peak VO2, % predicted, VE/VCO2, AT, workload, systolic BP < 130, HR recovery

- **Clinical Exam markers**
  - BP (admission and discharge), heart rate, JVP, +S3, cachexia
  - Depression
  - Obstructive sleep apnea

- **Echo parameters**
  - EF, chamber size (LV, LA, RA), sphericity,
  - RNA
  - RVEF, LVEF

- **Recurrent hospitalizations**

- **ECG**
  - IVCD

- **Hemodynamic markers**
  - PA pressures, CO, CI, MVO2

- **Endomyocardial biopsies**
  - Microarrays transcriptomic biomarkers

- **Marital status**
World population pyramids
Canada’s Aging Population – The baby boomers

Age: 65 yrs and over

% of population >65 yrs old
Aging population

- US/Canada Statistics
  - The proportion of the population that is >65 years of age will double in the next 20 years.
  - Need to understand outcomes in this patient population

- It used to be that transplants would only be done patients <50 years of age

- Some centers viewed advanced age as a contraindication to consideration of advanced therapies and namely transplantation
HF in the real world:

What the “average” HFrEF patient looks like

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75 years</td>
</tr>
<tr>
<td>Female</td>
<td>52%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>31%</td>
</tr>
<tr>
<td>COPD</td>
<td>31%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>30%</td>
</tr>
</tbody>
</table>

Gheorghiade, 2005
Therapeutic Approach to Patients With HFrEF

Patient with LVEF ≤ 40% and Symptoms

- Triple therapy ACEi (or ARB if ACEi intolerant), BB, MRA
  - Titrate to target doses or maximum tolerated evidence-based dose

REASSESS SYMPTOMS

- NYHA I
  - Continue triple therapy

- NYHA II–IV: SR, HR ≥ 70 bpm
  - Add ivabradine and switch ACEi or ARB to ARNI for eligible patients

- NYHA II–IV: SR with HR < 70 bpm or AF or pacemaker
  - SWITCH ACEi or ARB to ARNI for eligible patients

REASSESS SYMPTOMS AND LVEF

Nonpharmacologic therapies (teaching self-care, exercise)

Diuretics to Relieve Congestion

Titrated to minimum effective dose to maintain euvoledema

Advance Care Planning and Documentation of Goals of Care

CCS HF guidelines

The promise of a healthy heart.

TED ROGERS CENTRE FOR HEART RESEARCH
The spectrum of HF

ACC/AHA

Stage A
High risk, no symptoms

Stage B
Structural disease, no symptoms

Stage C
Symptomatic

Stage D
Refractory symptoms, very advanced HF

NYHA

Class I
No symptoms

Class II
Limited with activity

Class III
Limited with less than ordinary activity

Class IV
Severely limited any activity, worsens symptoms

INTERMACS

Disease Trajectory

Walking wounded

Housebound

Frequent hospitalizations

Inotrope dependent

Sliding on inotropes

Crash and burn

Risk of hospitalization for AHF

The promise of a healthy heart.
Dilemmas of Transplantation vs LVAD

**Transplantation**
- ‘Selective’ patient selection
- Not readily available
- Limited donor pool
- Consequences of immunosuppression

**LVAD**
- Driveline exit site
- Adverse events
- Batteries
- Durability of device
Transplant (VAD) workup

- CPET testing (Class 1B)
- RHC (Class 1C) +/- vasodilator challenge
- Co-morbidities
  - Age, BMI <35, cancer, DM, CKD, PVD, tobacco use, substance abuse (cannabis), psychosocial, frailty
  - “Carefully selected patients >70 years of age may be considered for cardiac transplantation. For centers considering these patients, the use of an alternate-type program (i.e., use of older donors) may be pursued (Class IIb, Level of Evidence: C).”

ISHLT 2016 – listing criteria 10-year update
Positives in patients ≥ 70 y.o.

- More mature and compliant
- Less likely to derive a driveline injury (less active)
- More accepting of inherent lifestyle limitations presented by LVAD support
- Appreciative of the improved quality of life
- Have supportive adult children willing to assist in care
- Financial stability
Precautions in patients ≥ 70 y.o.

- Poor eye sight
- Decreased manual dexterity
- Older care givers
- Higher rate of co-morbidities
Transplant in older patients
Age distribution of heart transplant recipients

UNOS data – Jan 1998 to June 2010
Defining 2 age groups: 60-69; >70
11,307 patients >60 y.o. (including 445 >70 y.o.)

Goldstein et al. JHLT. 2012 31:679-685
Age distribution of heart transplant recipients

UNOS data – Jan 1987 to June 2014
Defining 2 age groups: 60-69; >70
50,432 patients (including 715 >70 y.o.)

Cooper et al JHLT 2016
UNOS registry

Table 4 Multivariate Predictors of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 70 years</td>
<td>1.289 (1.039–1.6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Male recipient</td>
<td>0.81 (0.7–0.936)</td>
<td>0.004</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.009 (1.005–1.013)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>ABO match vs identical</td>
<td>1.218 (1.055–1.406)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diagnosis vs DCM</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.237 (1.089–1.404)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.999 (0.84–1.188)</td>
<td></td>
</tr>
<tr>
<td>Recipient diabetes</td>
<td>1.248 (1.113–1.399)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Ventilator support</td>
<td>1.75 (1.345–2.277)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.02 (1.011–1.028)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.144 (1.088–1.203)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.245 (1.977–5.325)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Ischemic time</td>
<td>1.064 (1.013–1.116)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio.

Median survival for age > 70 8.5 years

Goldstein et al. JHLT. 2012 31:679-685

UNOS OHT Survival 2005-2013
Age ≥ 70 versus < 70

Cooper et al JHLT 2016
ISHLT registry - 30d mortality

64,354 heart transplants, 1988-2013
Estimated effect of donor (A) and recipient (B) age on 30-d mortality
Univariant logistic regression model

Bergenfeldt et al JHLT 2019
Post-transplant survival stratified by age – 10 year follow-up

52,995 recipients – ISHLT registry 1995-2011

Wever-Pinzon et al, JHLT 2017

Post-transplant survival stratified by age

Conditional post-transplant survival stratified by age
Risk of cause-specific mortality

ISHLT registry captures 65% of all heart transplants performed world-wide

Confirmation that age >70 at the time of transplant is associated with increased risk of death

Interestingly, at 3 and 5 years post-transplant, fewer patients had different strategies of IS

Wever-Pinzon et al, JHLT 2017
Another way to look at the data

Kaplan-Meier survival curves of post-transplant mortality for donor-recipient age 64,354 heart transplants, 1988 – 2013 ISHLT registry
Recipient age associated with longer term mortality
Older donor age was associated with higher mortality at all f/u time points

Bergenfeldt et al JHLT 2019
LVAD in older patients
Important things to consider

Patient Characteristics
- Age
- Size
- Blood type
- Hemodynamic stability
- Associated illnesses

Center Specific Data
- Wait times
- Adverse events
LVAD implantation – INTERMACS data

From 2008-2017 – 18,539 patients with LVADs
20% females

Based on Intermacs Profile

Kormos et al., JHLT 2019
Age - independent risk factor for DT-LVAD

Age 60 to 70
Hazard ratio for death: 1.78 (p < 0.0001)

Kirklin et al., JHLT 2011
# DT-VAD in older patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Description of study cohort</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 Kim et al. [52]</td>
<td>Retrospective cohort study (MCSRNI)</td>
<td>&gt;70 years (163); &lt;70 years (986)</td>
<td>Overall survival of &gt;70 was similar to &lt;70-year group</td>
</tr>
<tr>
<td>2013 Atluri et al. [53]</td>
<td>Retrospective INTERMACS (2006–2012)</td>
<td>5029 patients; 4439 &lt;70 years and 590 &gt;70 years</td>
<td>Age was not a significant factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only 19% of the 590 were BTT</td>
<td>But most powerful predictor was preoperative creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Older patients had increased GI bleeding incidence</td>
</tr>
<tr>
<td>2011 Adamson et al. [22]</td>
<td>Retrospective analyses</td>
<td>55 patients; 30 &gt;70 years</td>
<td>Older group had similar length of stay and bypass time</td>
</tr>
<tr>
<td>2015 Grady et al. [61]</td>
<td>Retrospective INTERMACS 2010–2012</td>
<td>&lt;60 years 457; 60–69 years 520; &gt;70 years 493</td>
<td>No difference in length of stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Survival at 1 month and 1 and 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QOL and functional status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or incidence of adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HRQOL was better in the older cohort, but magnitude of improvement was same</td>
</tr>
</tbody>
</table>

BTT: bridge to transplantation; GI: gastrointestinal; QOL: quality of life; HRQOL: health-related quality of life.

Nair and Gongora Exp. Rev. Cardiol. 2018
Age distribution of LVAD recipients

Thrombosis

Stroke

Bleeding

Survival

MCS Research Network - 1149 CF LVADS

Kim et al J. Card Failure 2016
Survival post-LVAD

- Advanced age as a dichotomized variable around age 70 is not a significant independent predictor of survival.
- When age is set as a continuous variable – predicts mortality with a 20% increase risk of death/10 years of life.
- Known that age is a strong predictor of GIB – age >65 associated with a 20-fold increased risk:
  - GIB is associated with increase risk for thromboembolic events.
- The most significant independent predictor of survival was creatinine.
- There is a 2-fold higher risk of death for every 0.1 mg/dL increase in creatinine.
**Age as an independent risk factor for death among LVAD recipients**

Survival by Age Groups

- **Age < 50 yrs**: n = 1453; Deaths = 228
- **Age 50-64 yrs**: n = 2493; deaths = 505
- **Age 65-70 yrs**: n = 832; deaths = 210
- **Age > 70 yrs**: n = 656; Deaths: n = 177

*Overall p < 0.0001*

Event: Death (censored at transplant and recovery)

**Freedom from adverse events after LVAD stratified by age**

- **<50 yrs**: n = 1453; Events = 947
- **≥65 yrs**: n = 1490; Events = 1010

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

p = 0.02

Kirklin et al., JHLT 2013
Clinical Strategies and Outcomes in Advanced Heart Failure Patients Older Than 70 Years of Age Receiving the HeartMate II Left Ventricular Assist Device

A Community Hospital Experience

Robert M. Adamson, MD, Marcia Stahovich, RN, Suzanne Chillcott, BSN, Sam Baradarian, MD, Joseph Chammas, MD, Brian Jaski, MD, Peter Hoagland, MD, Walter Dembitsky, MD

San Diego, California

Objectives

The primary objective of this study was to determine outcomes in left ventricular assist device (LVAD) patients older than age 70 years.

Background

Food and Drug Administration approval of the HeartMate II (Thoratec Corporation, Pleasanton, California) LVAD for destination therapy has provided an attractive option for older patients with advanced heart failure.

Methods

Fifty-five patients received the HeartMate II LVAD between October 5, 2005, and January 1, 2010, as part of either the bridge to transplantation or destination therapy trials at a community hospital. Patients were divided into 2 age groups: \( \geq 70 \) years of age (\( n = 30 \)) and \(<70 \) years of age (\( n = 25 \)). Outcome measures including survival, length of hospital stay, adverse events, and quality of life were compared between the 2 groups.

Results

Pre-operatively, all patients were in New York Heart Association functional class IV refractory to maximal medi-
Community experience

No significant differences in survival, LOS, functional status improvement or adverse events (55 patients).

Adamsom et al., JACC 2011
Pre-operative risk factors for outcomes

Boyle et al 2014

- Retrospective
- Patients with HMII as part of DT or BTT clinical trials
  - 2005 – 2010
  - 1,302 patients (956 patients included in the analysis)
  - 2 years follow-up
Effects of Gender and Age

Older age, and its associated risk of GIB has been well documented.

This analysis showed older patients were at a higher risk of:
- bleeding events
- female gender
- anemia before surgery
- risk of stroke (females)

Boyle et al, JACC 2014
LVAD vs Transplant
LVAD vs OHT

Single centre – Columbia

- 19 LVAD vs 28 OHT
- LVAD patients were older (72yo vs 68 yo)
- 1 year survival similar
- LVAD group had a longer ICU and total length of stay

Conclusions: Survival rates during the first year following surgery in LVAD patients are excellent and comparable to those seen in OHT recipients older than 65 years of age at our institution. Postoperative ICU stay and total postoperative stay were significantly longer in the LVAD group.

Abstract - Melnitchouk et al., JHLT 2011
Survival: HeartMate II vs Transplant

Survival (%)

- Age < 70 (N=122)
- Age >=70 (N=74)

P (log-rank) = 0.016
Hazard Ratio (LVAD) = 2.9 (1.8 - 7.3)
P (adjusted for age) = 0.059

Adamson et al., 2011; unpublished
INTERMACs – Cumulative incidence

post-VAD mortality

post-VAD transplantation

post-VAD recovery

Aleksova et al, unpublished data 2019
## Complications post-VAD

<table>
<thead>
<tr>
<th>Adverse event type</th>
<th>Cause-specific HR for age of 70 or above [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI bleeding</td>
<td>1.200 [1.089, 1.322]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>0.962 [0.886, 1.044]</td>
<td>0.35</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.858 [0.741, 0.992]</td>
<td>0.039</td>
</tr>
<tr>
<td>Pump-related thrombosis</td>
<td>1.247 [0.408, 3.813]</td>
<td>0.70</td>
</tr>
<tr>
<td>Pump exchange</td>
<td>0.683 [0.562, 0.830]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>0.690 [0.532, 0.894]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Aleksova et al, unpublished data 2019
Things to consider

- Older patient population is growing.
- Heart failure is an epidemic associated with a need to consider advanced therapies in older patients.
- Heart transplantation is resource limited.
- Age does affect outcomes post-transplant (median survival 8.5 years, age >70 y.o.)
- DT-LVAD numbers are growing
- LVAD outcomes is affected by age but patients >70 y.o. do well BUT we have VAD-related complications to consider
Conclusions

“Aging” does not equate to being frail nor does youth guarantee good health.

“Chronologic Age” cannot be a strict discriminator for patients that need advanced therapies.

The decision regarding “older patients” should be made with careful consideration.

It is still unknown whether age-based treatment policies in primary/secondary care reflect prejudices against older people.
Questions?

TedRogersResearch.ca
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Partners in the Ted Rogers Centre for Heart Research