The promise of a healthy heart.

VAD or heart transplantation after age 65

TED ROGERS CENTRE FOR HEART RESEARCH

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Disclosure Slide

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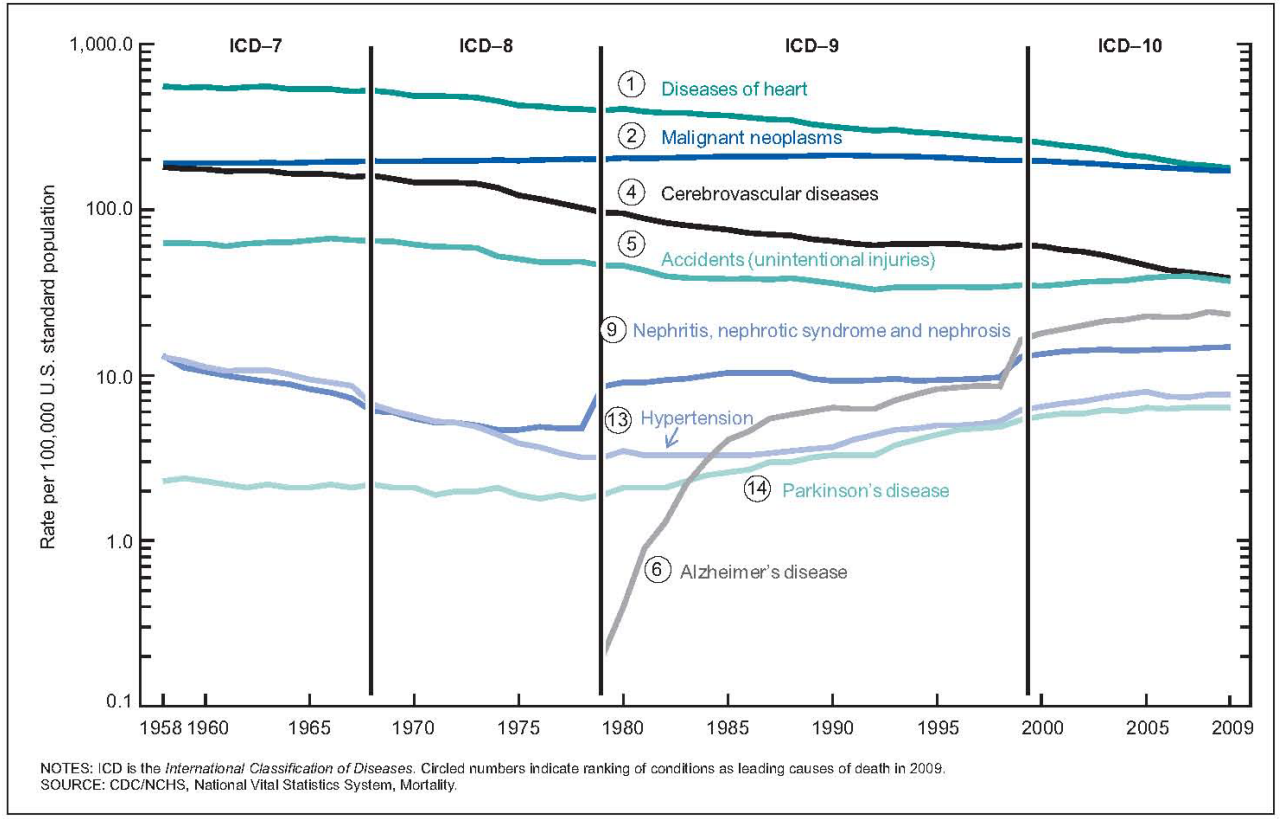
- I will NOT discuss off-label uses of drugs

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



NOTES: ICD is the *International Classification of Diseases*. Circled numbers indicate ranking of conditions as leading causes of death in 2009.
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Figure 6. Age-adjusted death rates for selected leading causes of death: United States, 1958–2008

National Vital Statistics Reports 2011

THE STATE OF THE HEART IN CANADA

1 MILLION
CANADIANS ARE LIVING WITH HEART FAILURE.

50,000
new cases of heart failure are diagnosed each year, making it the most rapidly rising cardiovascular disease among Canadians.

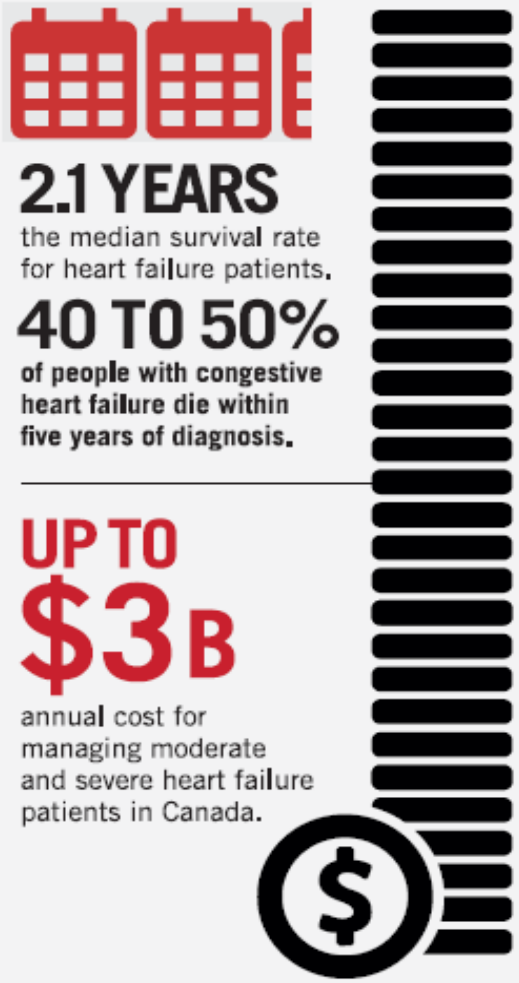
1 in 5
Canadians over the age of 40 have a risk of developing heart failure.

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

1.4 MILLION
HOSPITAL STAYS PER YEAR

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.



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.

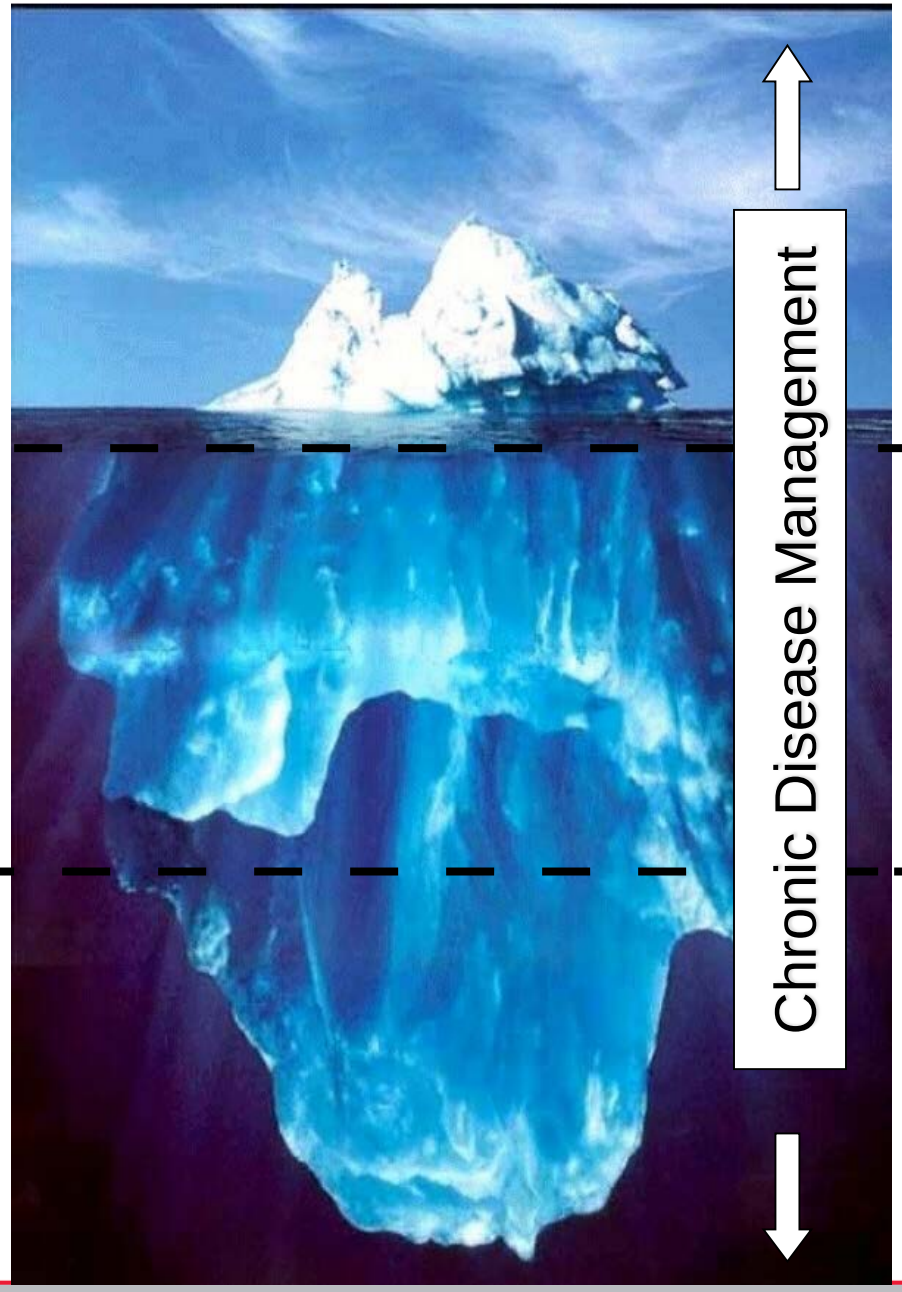
UP TO $3 B
annual cost for managing moderate and severe heart failure patients in Canada.

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.

~ 200 transplants
75 VADs

50 000
Advanced HF

500,000 with
HF diagnosis



Chronic Disease Management

Advanced therapies
Experimental Rx
Cardiac replacement

Tailored therapy
IV Vasodilators
IV diuretics
Optimization of oral therapy
Referral for CRT/ICD

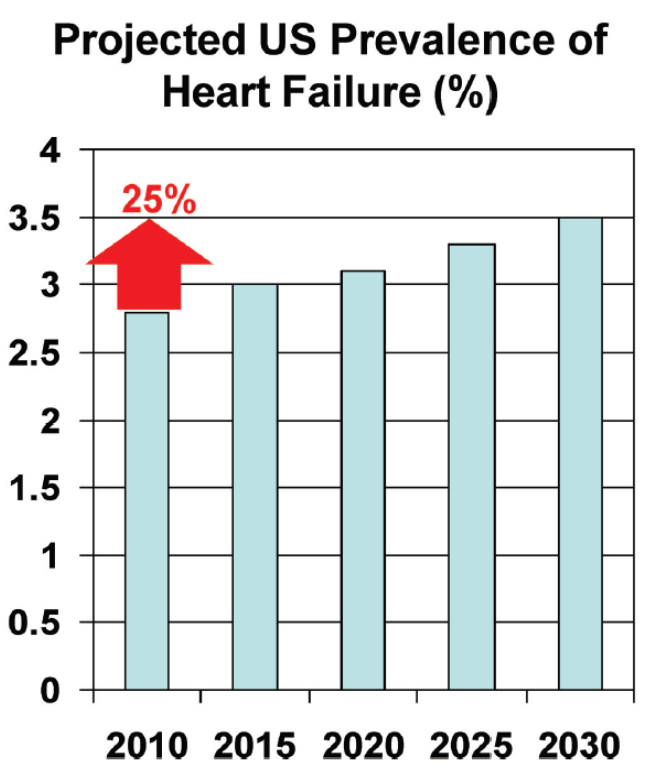
Aldosterone antagonist

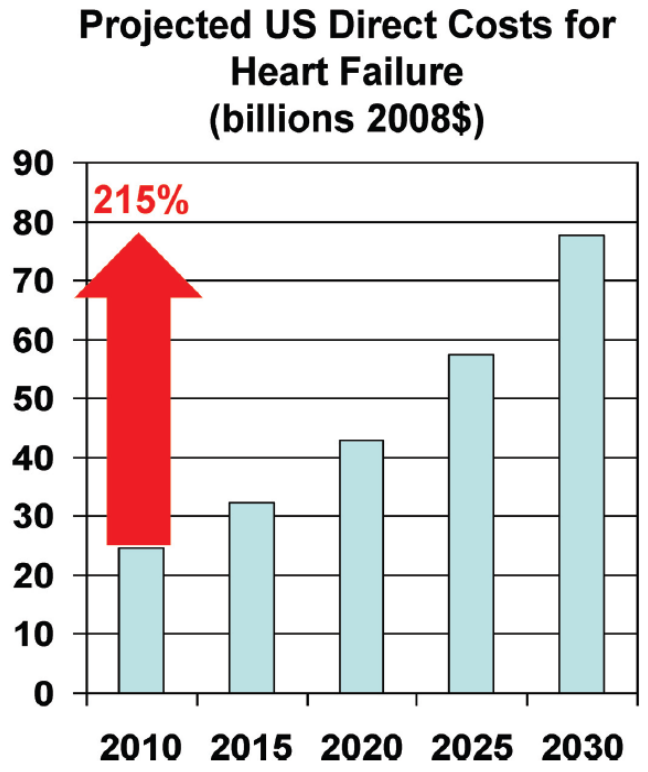
ACEi/ARB, Beta blocker
Diet, exercise prescription
Risk factor control

Projected US Heart Failure Prevalence and Direct Cost

Over the next 20 years:

- Prevalence will increase by 25%
- Annual direct medical costs will increase $77.7 billion (2008 dollars)



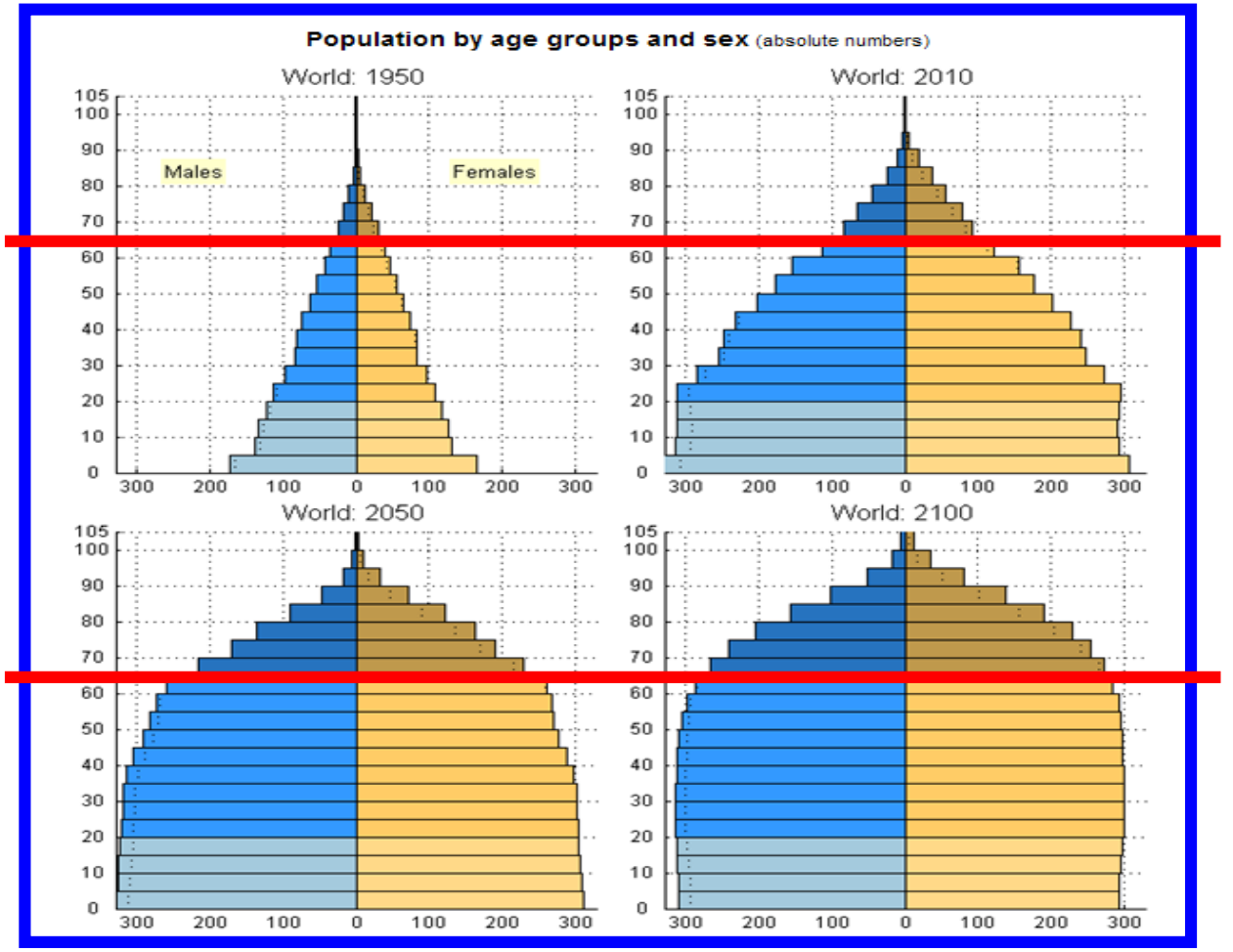


Konstam, Circulation. 2012

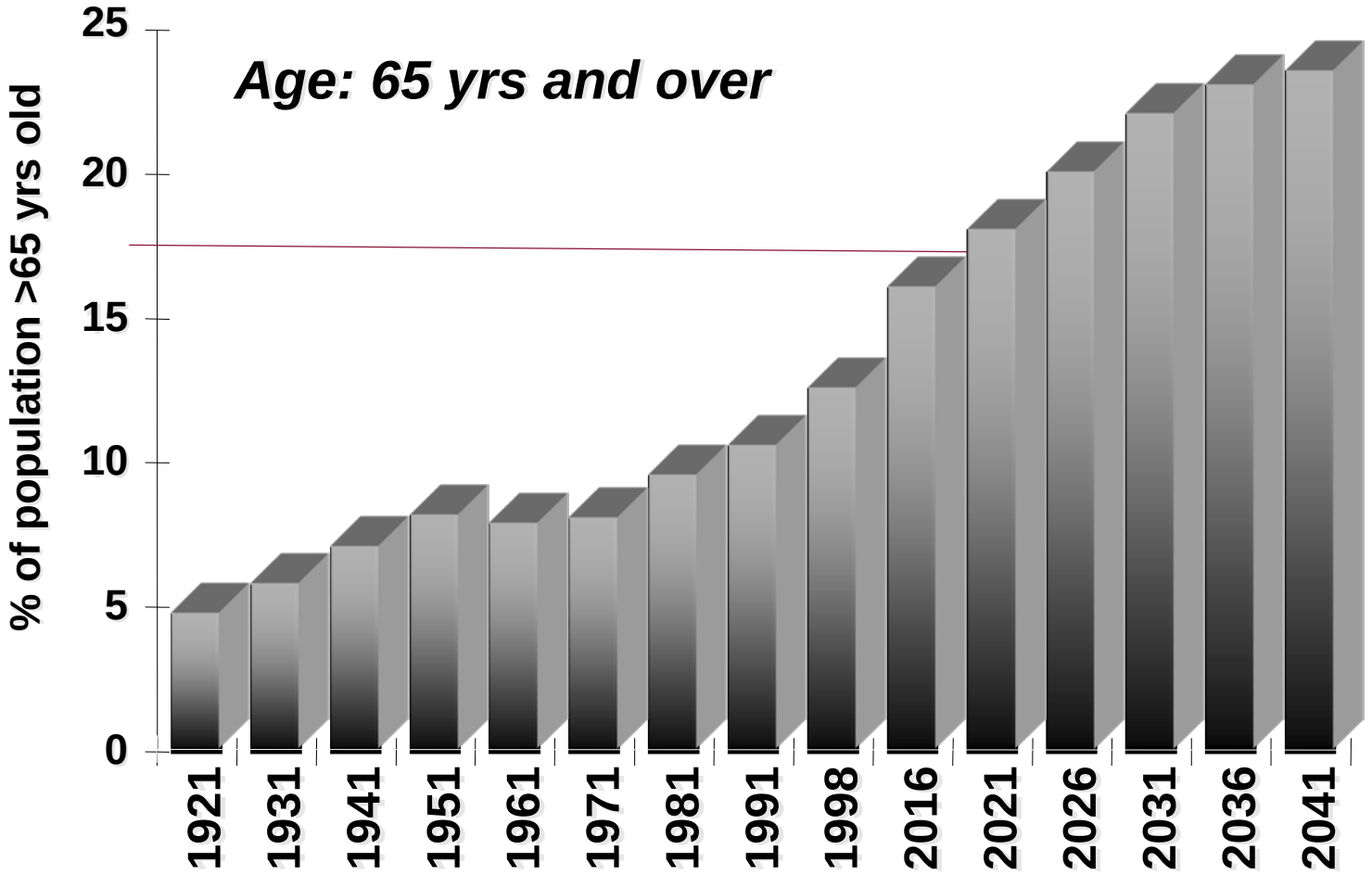
Prognostic Markers

- 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



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

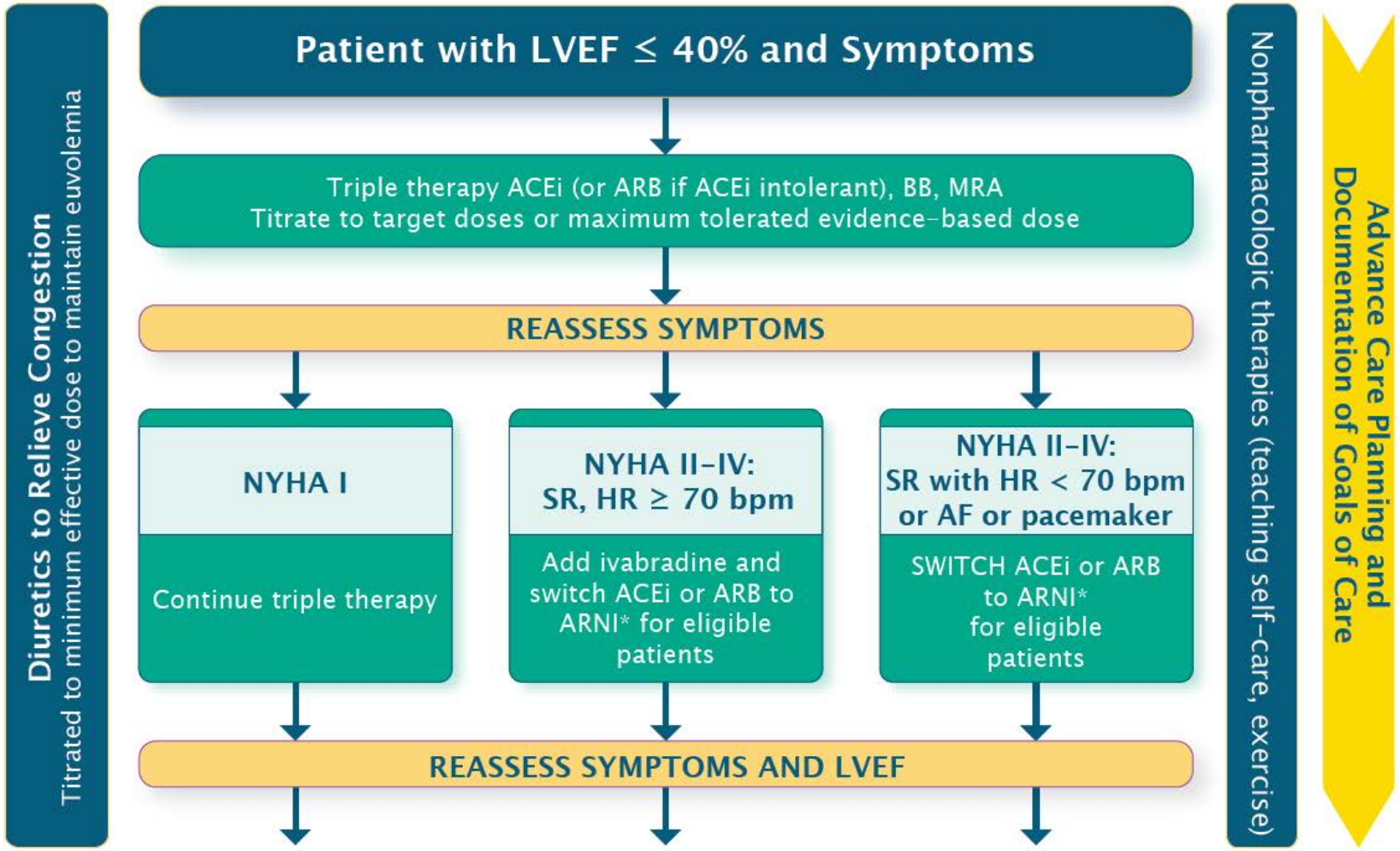
HF in the real world:

What the “average” HFrEF patient looks like

Age	75 years
Female	52%
Hypertension	72%
Diabetes	44%
Atrial fibrillation	31%
COPD	31%
Chronic kidney disease	30%

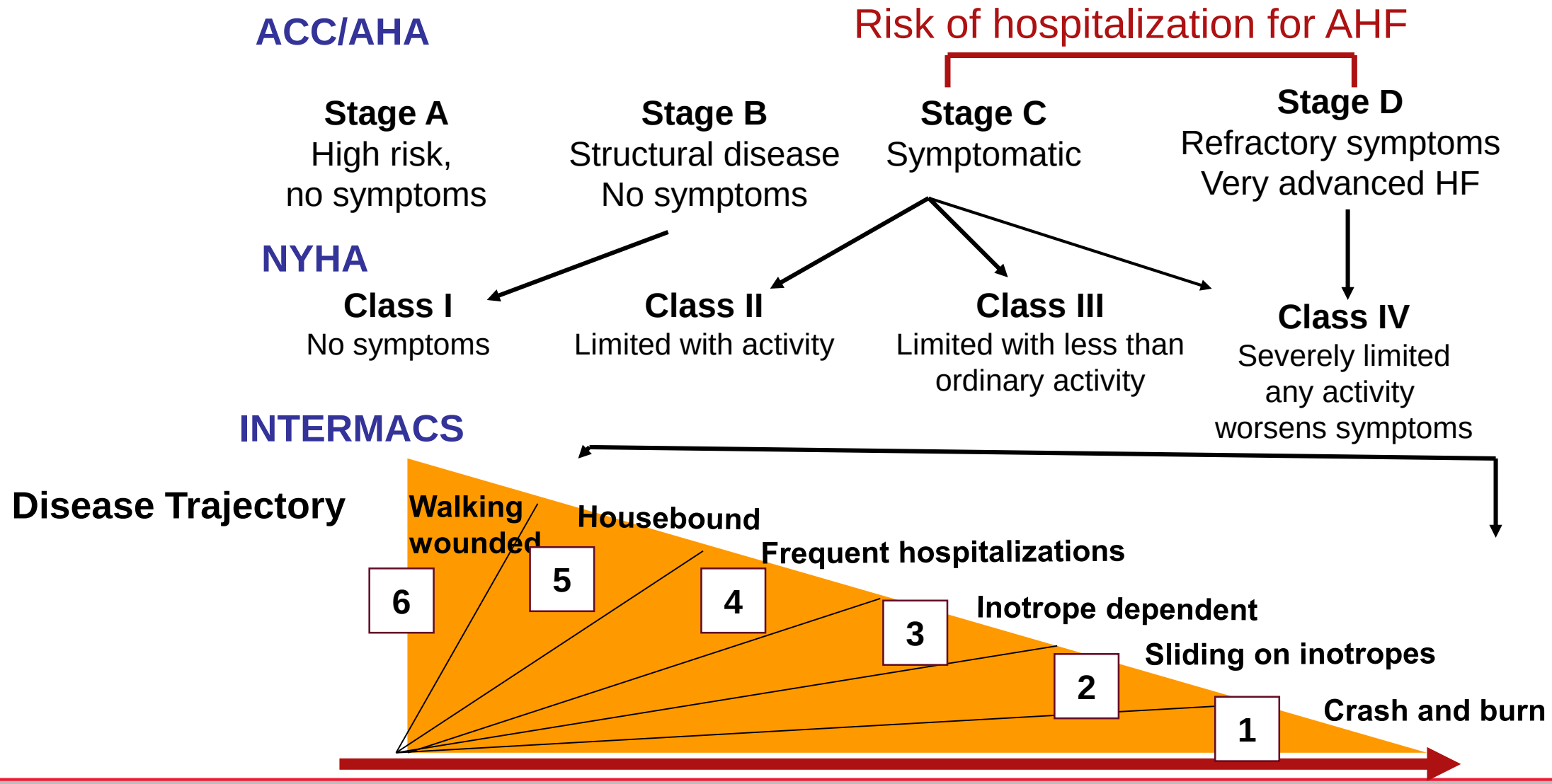
Gheorghiade, 2005

Therapeutic Approach to Patients With HFrEF



CCS HF guidelines

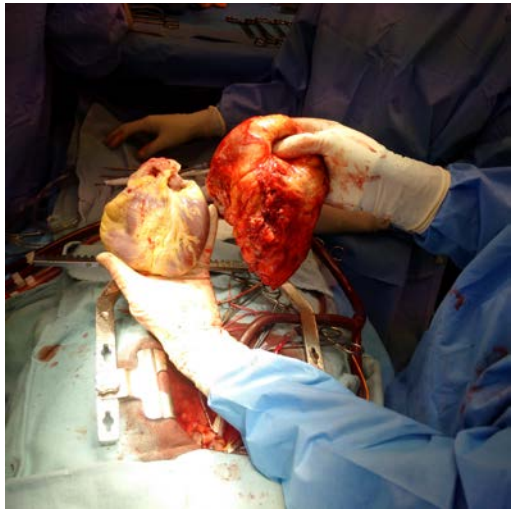
The spectrum of HF



Dilemmas of Transplantation vs LVAD

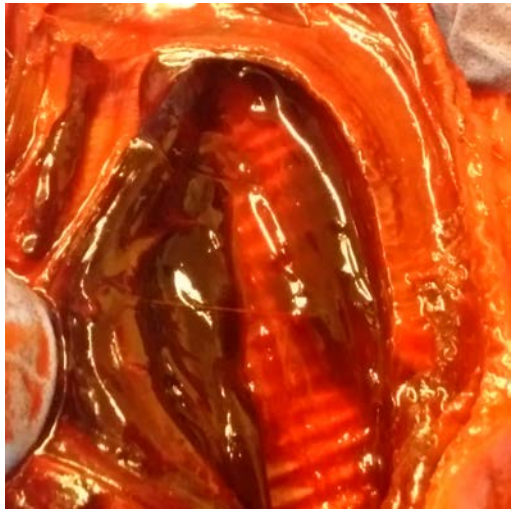
Transplantation

- ‘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.

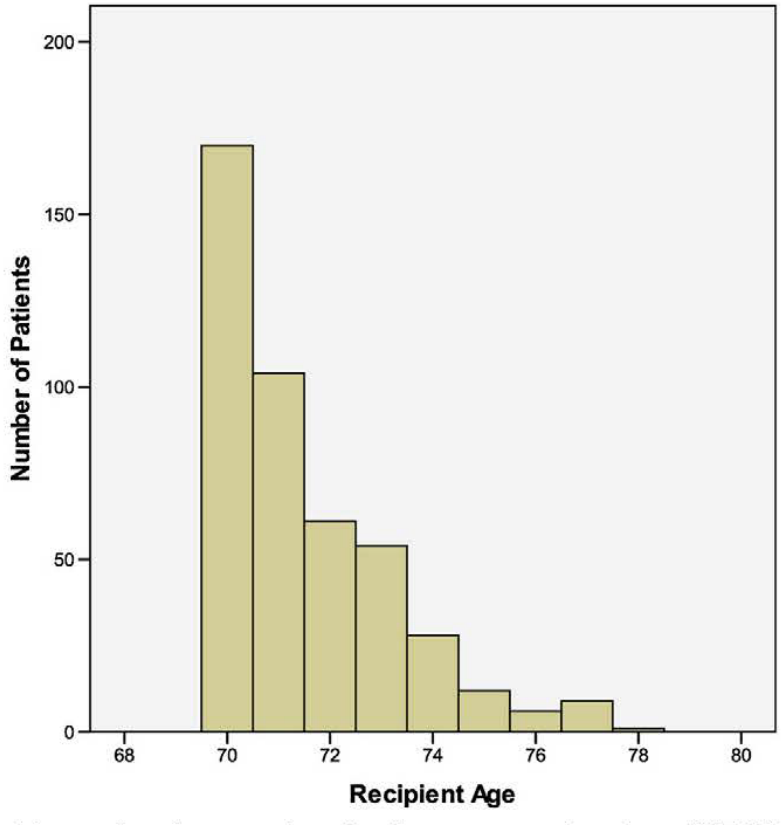
- More mature and compliant
- less likely to derive a driveline injury (less active)
- More accepting of inherent lifestyle limitations presented by LVAD support
- Appreciative of the improved quality of life
- Have supportive adult children willing to assist in care
- Financial stability

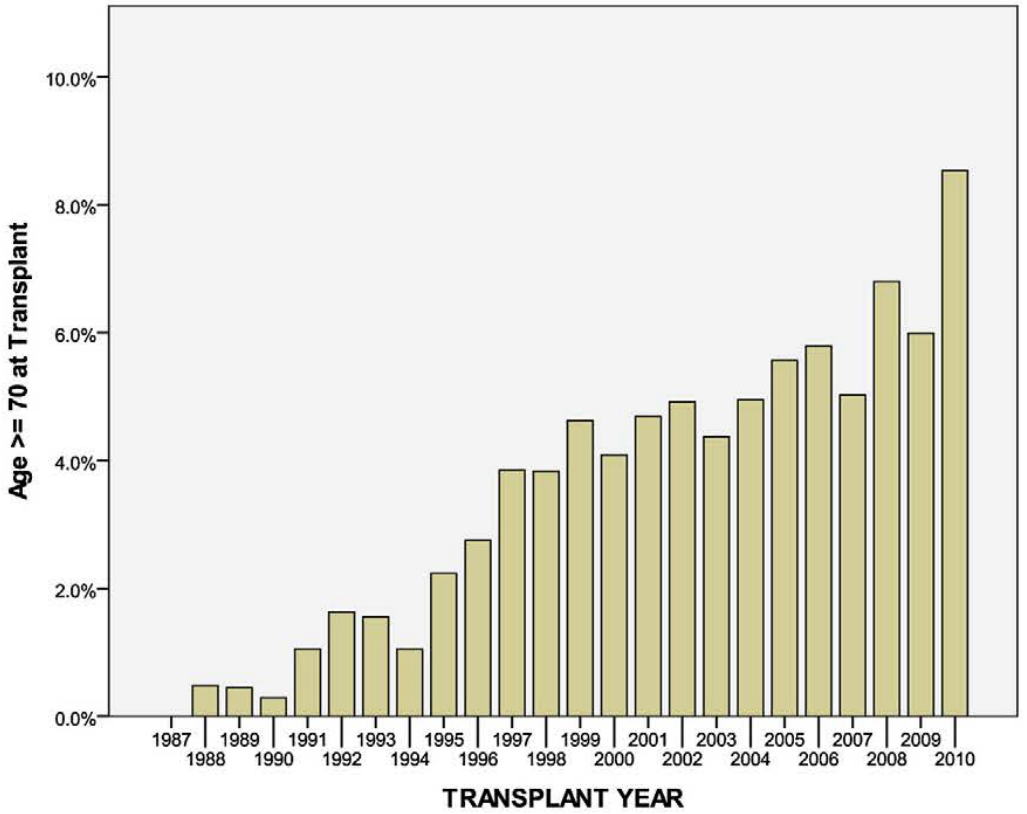
Precautions in patients ≥ 70 y.o.

- Poor eye sight
- Decreased manual dexterity
- Older care givers
- Higher rate of co-morbidities

Transplant in older patients

Age distribution of heart transplant recipients

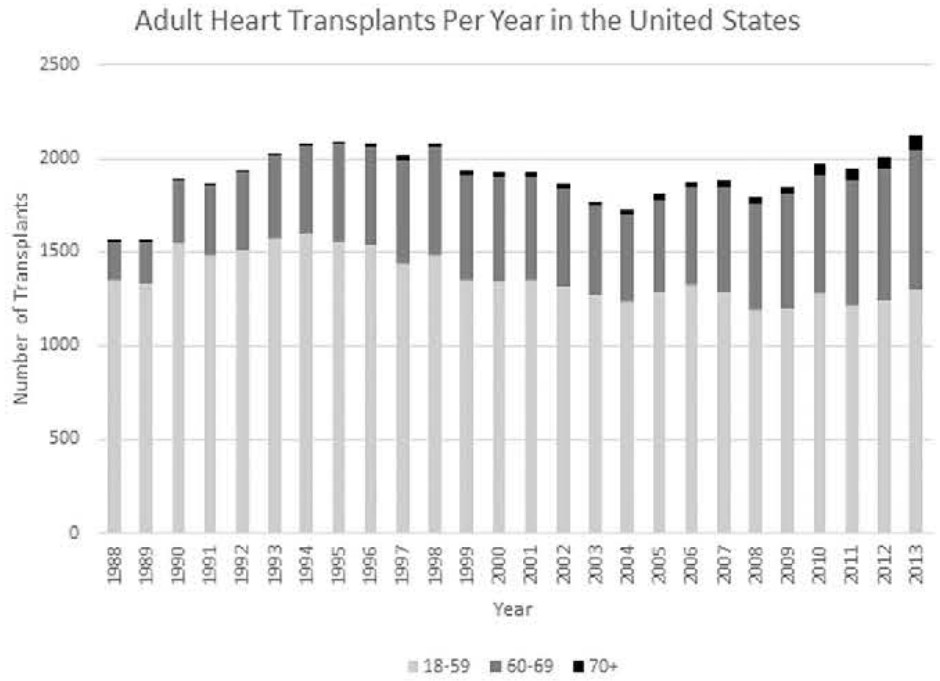


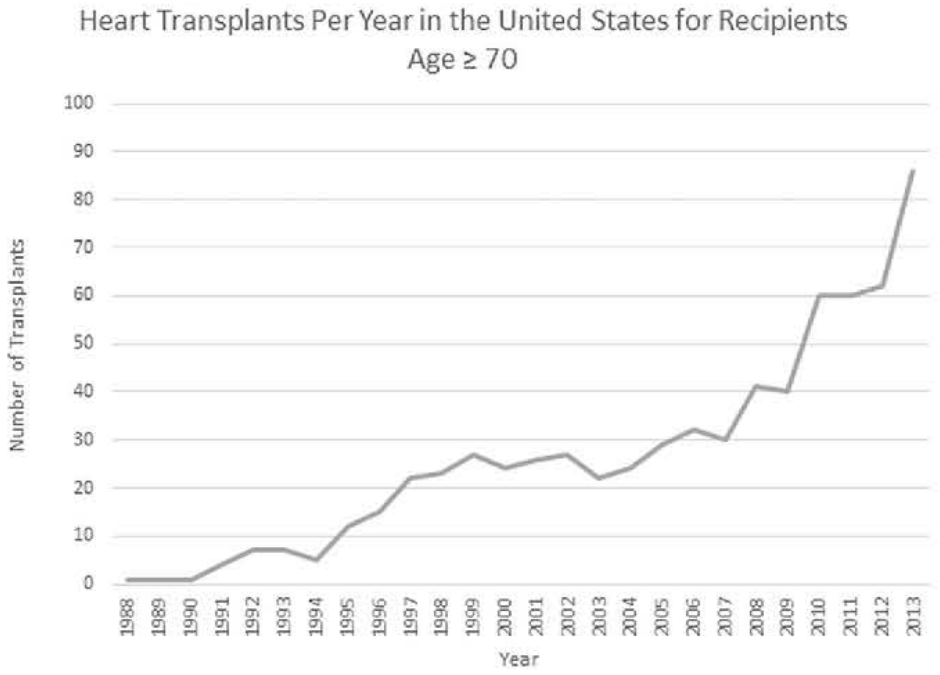


UNOS data – Jan 1998 to June 2010
Defining 2 age groups: 60-69; >70
11,307 patients >60 y.o. (including 445 >70 y.o.)

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.)

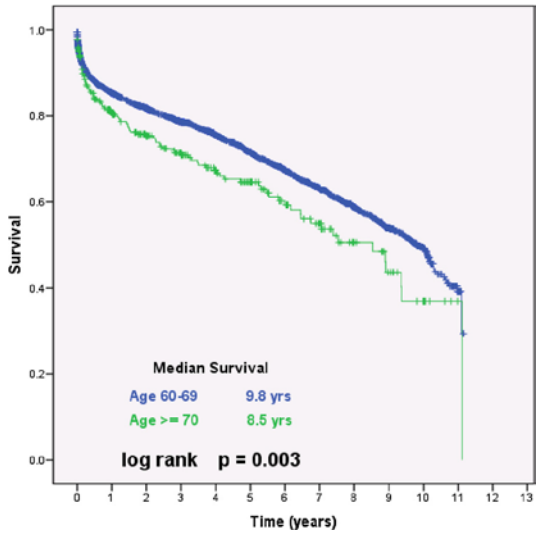
Cooper et al JHLT 2016

UNOS registry

Table 4 Multivariate Predictors of Death

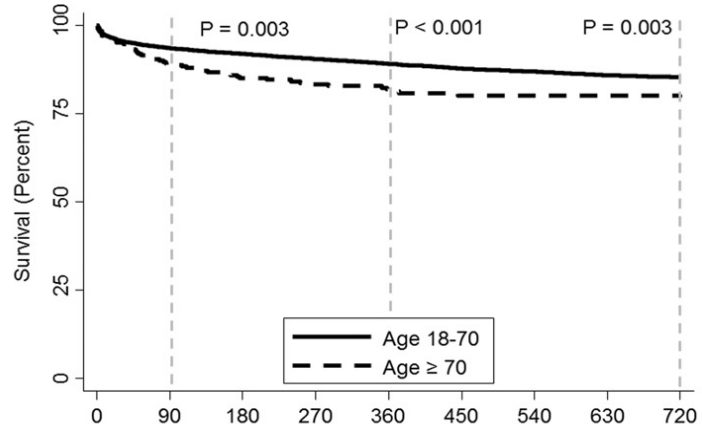
Variable	HR (95% CI)	*p*-value
Age ≥ 70 years	1.289 (1.039–1.6)	0.021
Male recipient	0.81 (0.7–0.936)	0.004
Donor age	1.009 (1.005–1.013)	<0.0005
ABO match vs identical	1.218 (1.055–1.406)	0.007
Diagnosis vs DCM		0.001
Ischemic	1.237 (1.089–1.404)	
Other	0.999 (0.84–1.188)	
Recipient diabetes	1.248 (1.113–1.399)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

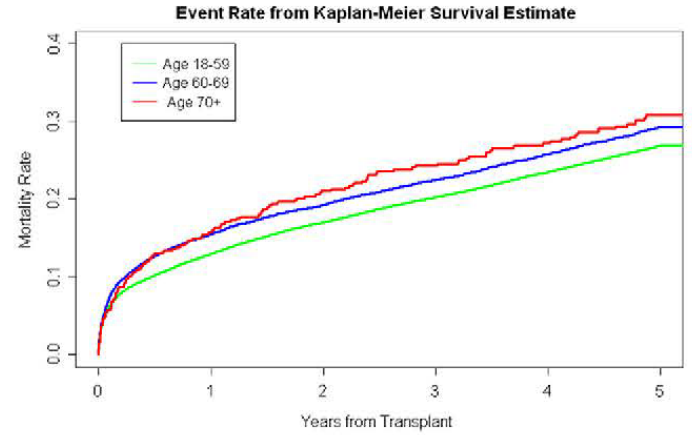
CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio.



Goldstein et al. JHLT. 2012 31:679-685
Median survival for age > 70 8.5 years

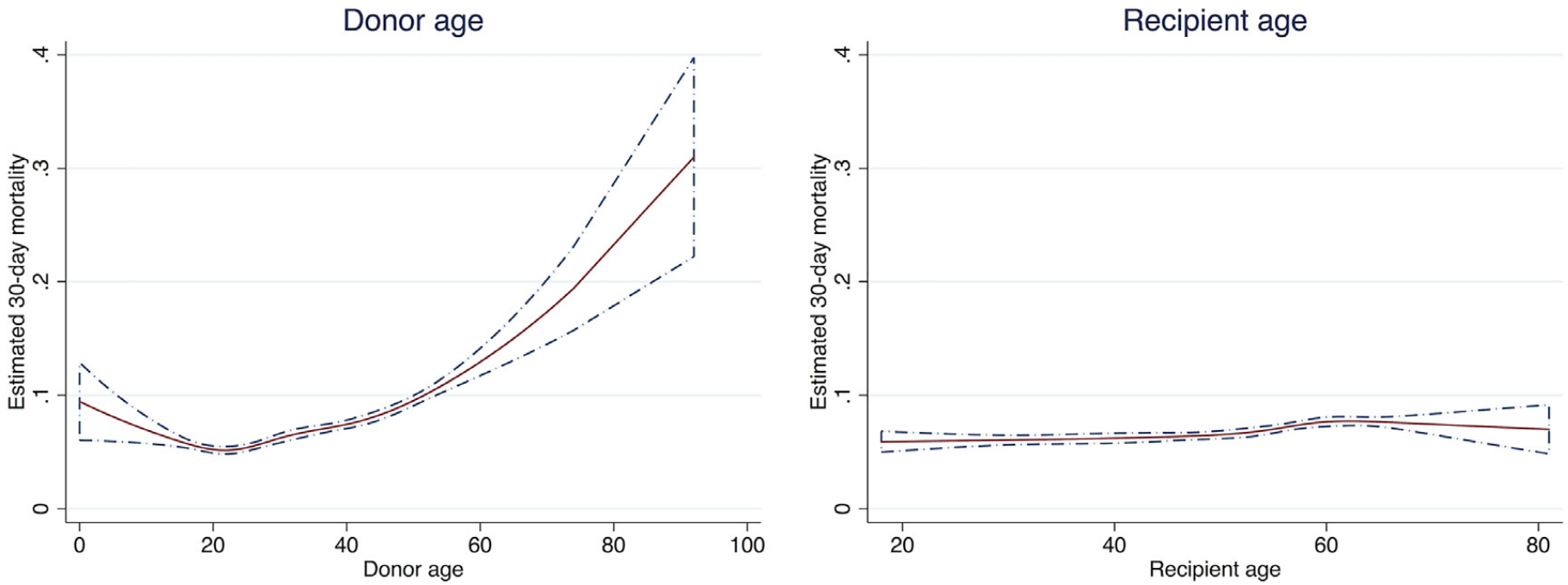
UNOS OHT Survival 2005-2013
Age ≥ 70 versus < 70
George. Ann Thorac Surg 2013





Cooper et al JHLT 2016

ISHLT registry - 30d mortality

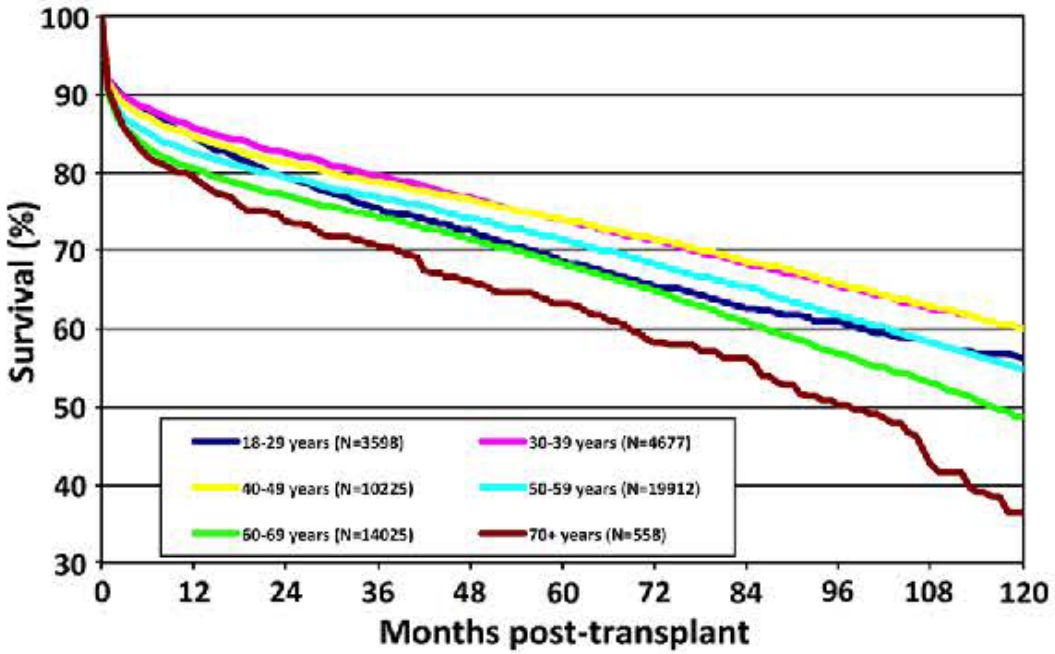


64,354 heart transplants, 1988-2013
Estimated effect of donor (A) and recipient (B) age on 30-d mortality
Univariant logistic regression model

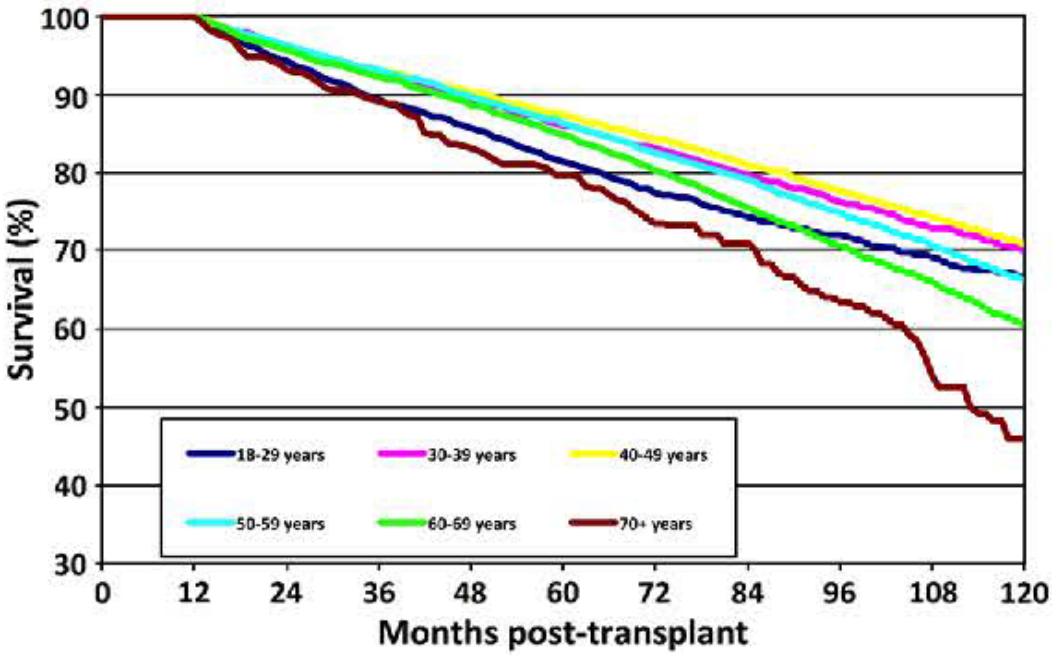
Bergenfledt et al JHLT 2019

Post-transplant survival stratified by age – 10 year follow-up

52,995 recipients – ISHLT registry 1995-2011



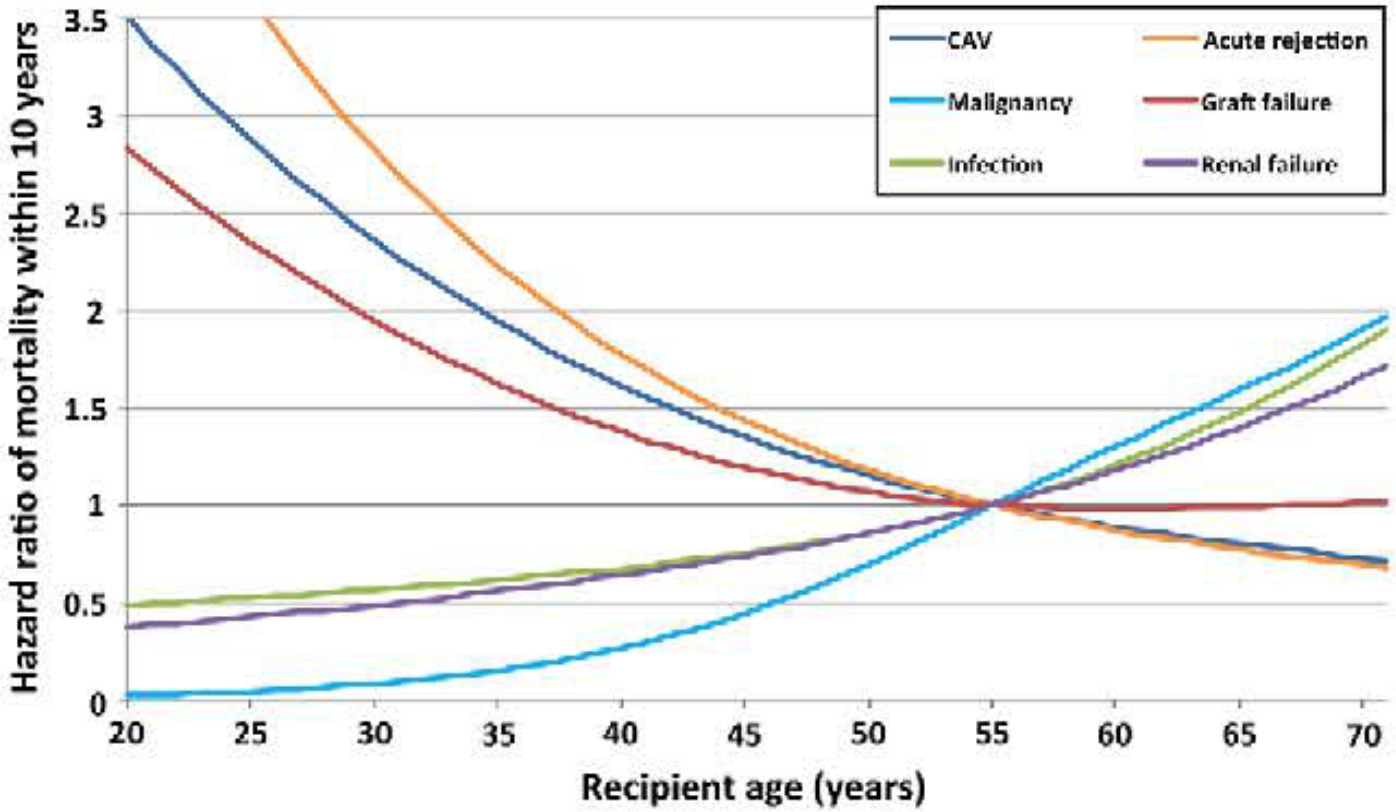
Post-transplant survival stratified by age



Conditional post-transplant survival stratified by age

Wever-Pinzon et al, JHLT 2017

Risk of cause-specific mortality



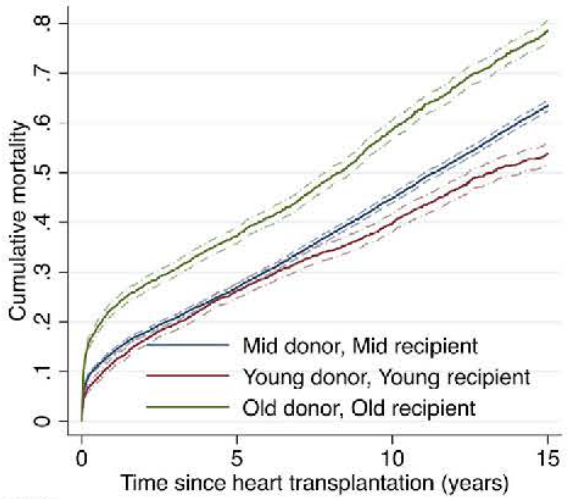
ISHLT registry captures 65% of all heart transplants performed world-wide

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

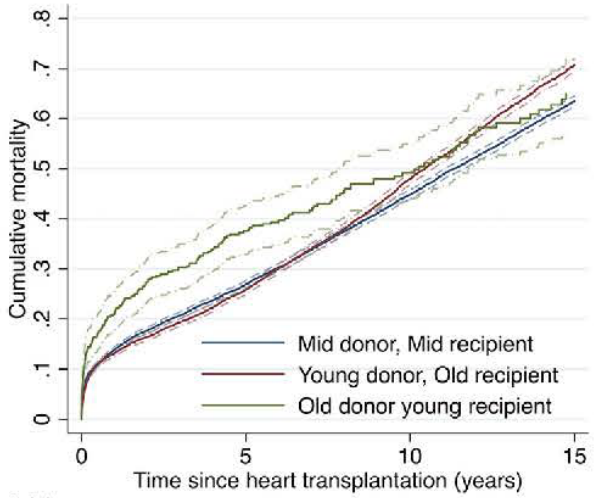
Interestingly, at 3 and 5 years post-transplant, fewer patients had different strategies of IS

Wever-Pinzon et al, JHLT 2017

Another way to look at the data



Patients at risk				
Mid donor, Mid recipient	14781	8222	4363	1899
Young donor, Young recipient	3834	2122	1158	545
Old donor, Old recipient	4020	1760	719	182



Patients at risk				
Mid donor, Mid recipient	14781	8222	4363	1899
Young donor, Old recipient	9537	5468	2752	989
Old donor, Young recipient	452	183	81	33

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

Bergenfledt et al JHLT 2019

LVAD in older patients

Important things to consider

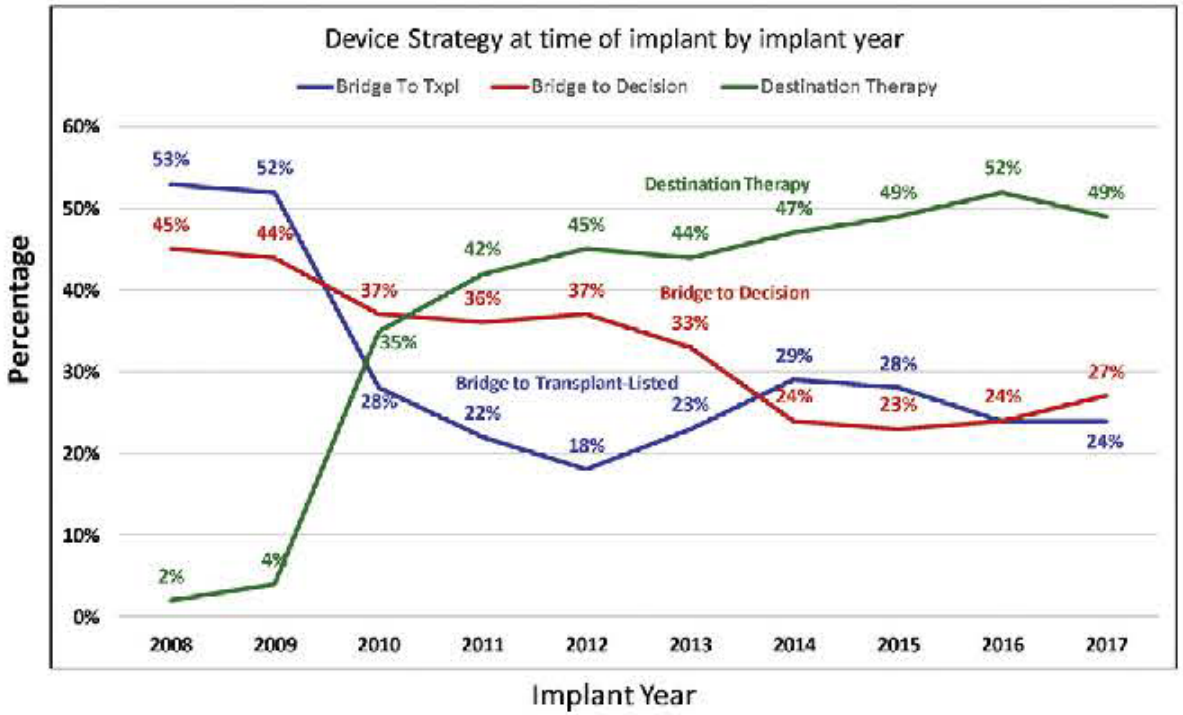
Patient Characteristics

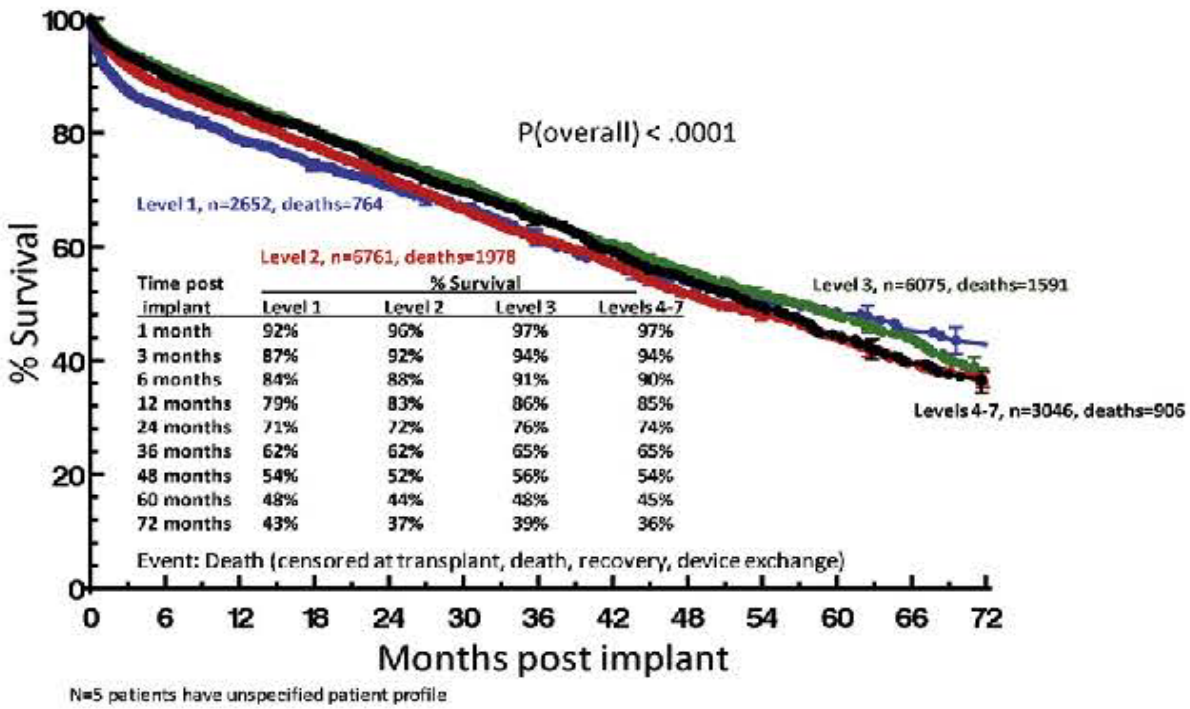
- Age
- Size
- Blood type
- Hemodynamic stability
- Associated illnesses

Center Specific Data

- Wait times
- Adverse events

LVAD implantation – INTERMACs data



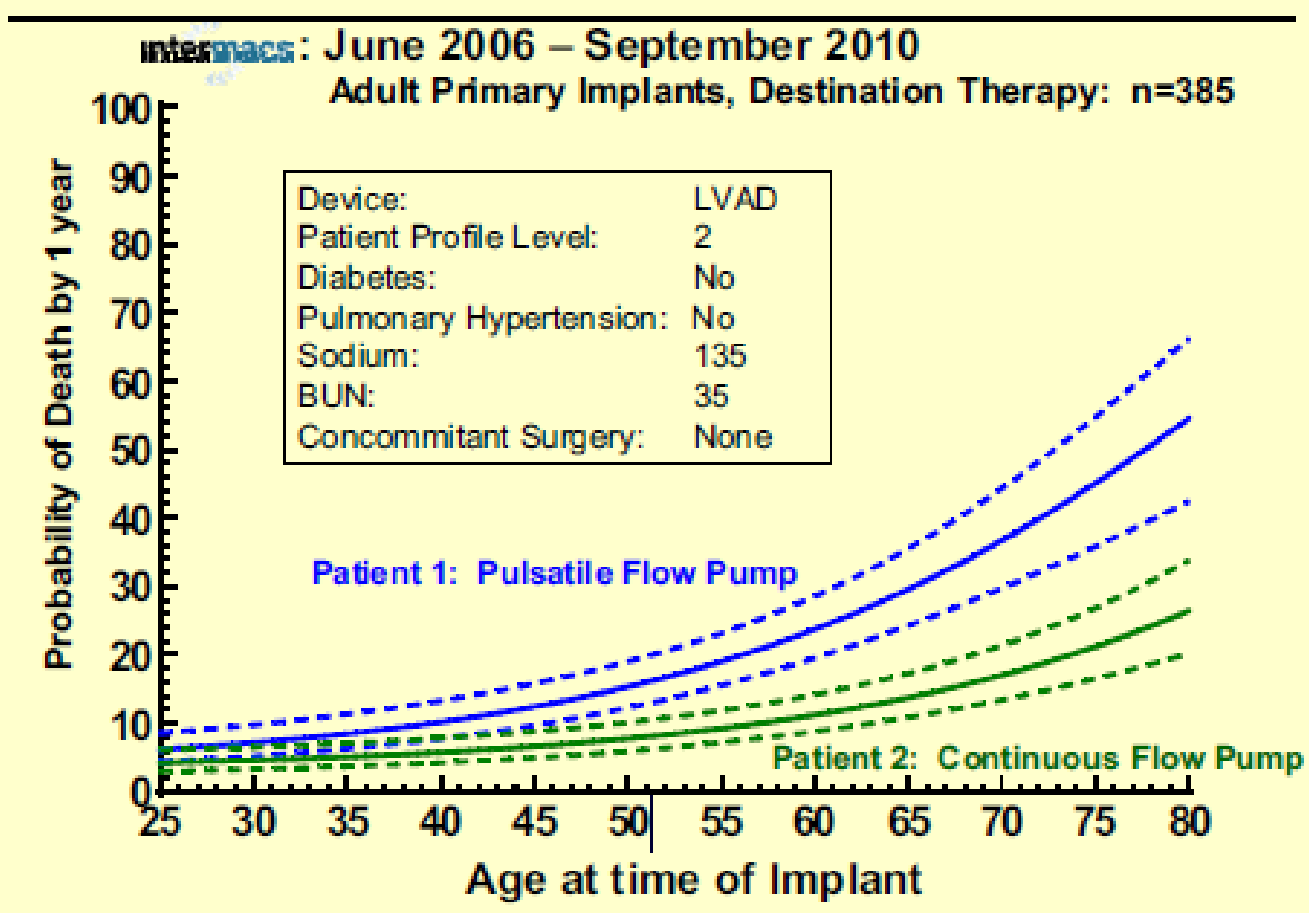


From 2008-2017 – 18,539 patients with LVADs
20% females

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

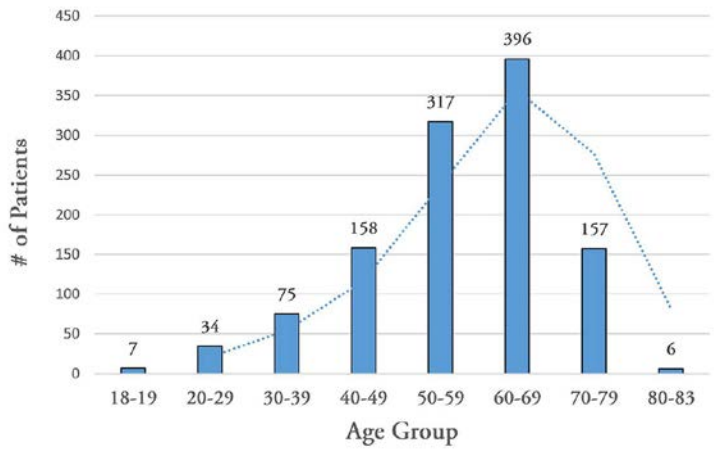
Table 2. Selected studies on destination therapy in older patients.

	Study	Study type	Description of study cohort	Conclusions
2016	Kim et al. [52]	Retrospective cohort study (MCSRN)	>70 years (163); <70 years (986) >70 years group 70% ischemic cardiomyopathy; 91% males; 6% BTT 4% prior sternotomy	Overall survival of >70 was similar to <70-year group Age was not a significant factor But most powerful predictor was preoperative creatinine Older patients had increased GI bleeding incidence
2013	Atluri et al. [53]	Retrospective INTERMACS (2006–2012)	5029 patients; 4439 <70 years and 590 >70 years Only 19% of the 590 were BTT	Age was a significant factor Older group had similar length of stay and bypass time 2-year survival was lower in age >70
2011	Adamson et al. [22]	Retrospective analyses	55 patients; 30 >70 years	No difference in length of stay Survival at 1 month and 1 and 2 years QOL and functional status or incidence of adverse events
2015	Grady et al. [61]	Retrospective INTERMACS 2010–2012	<60 years 457; 60–69 years 520; >70 years 493	HRQOL was better in the older cohort, but magnitude of improvement was same

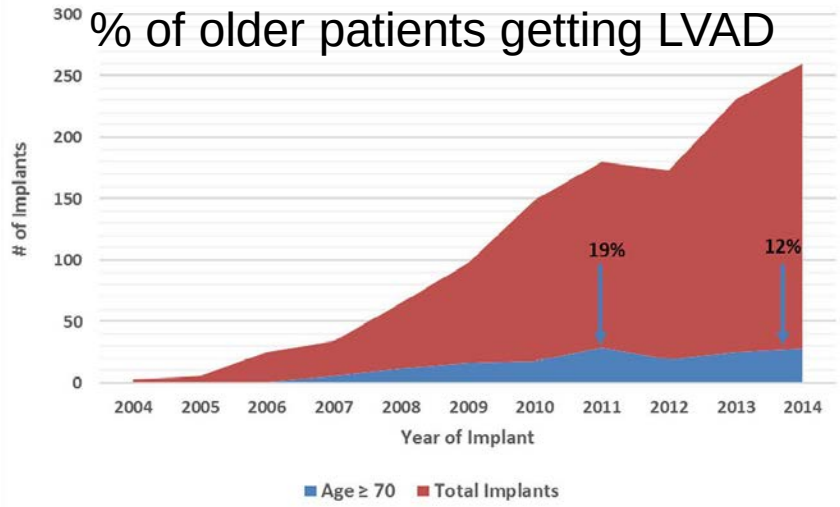
BTT: bridge to transplantation; GI: gastrointestinal; QOL: quality of life; HRQOL: health-related quality of life.

Nair and Gongora Exp. Rev. Cardiol. 2018

Age distribution of LVAD recipients

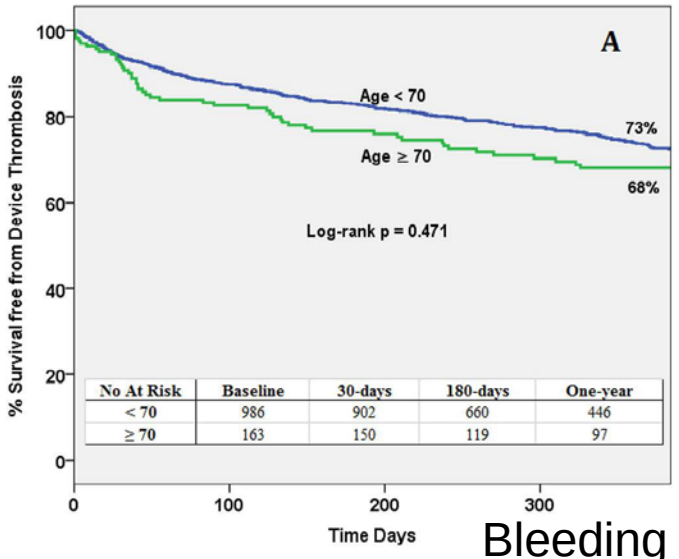


% of older patients getting LVAD

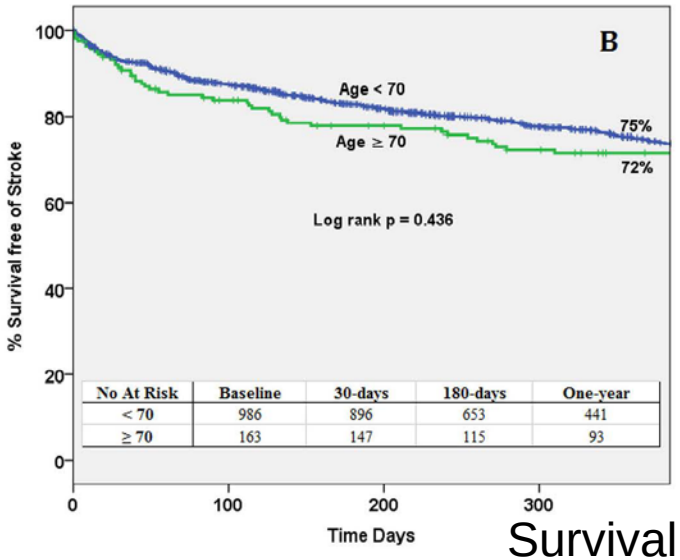


MCS Research Network - 1149 CF LVADS

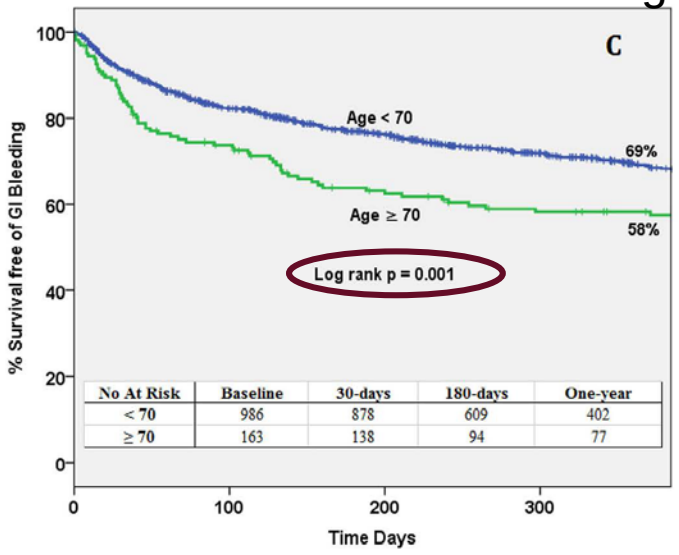
Thrombosis



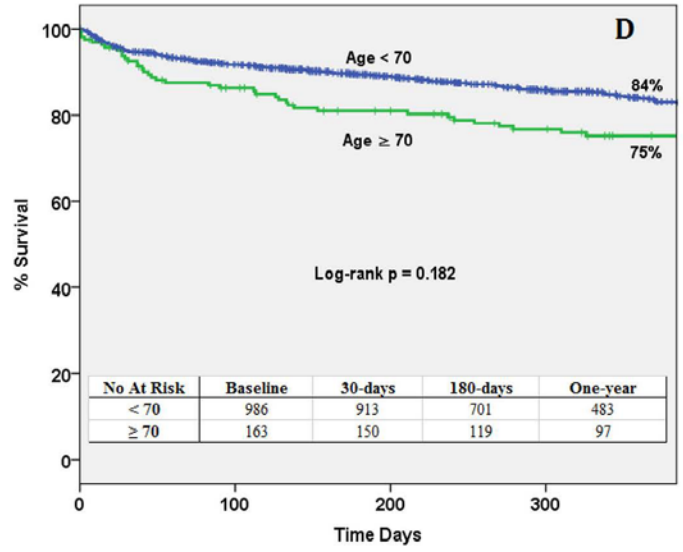
Stroke



Bleeding



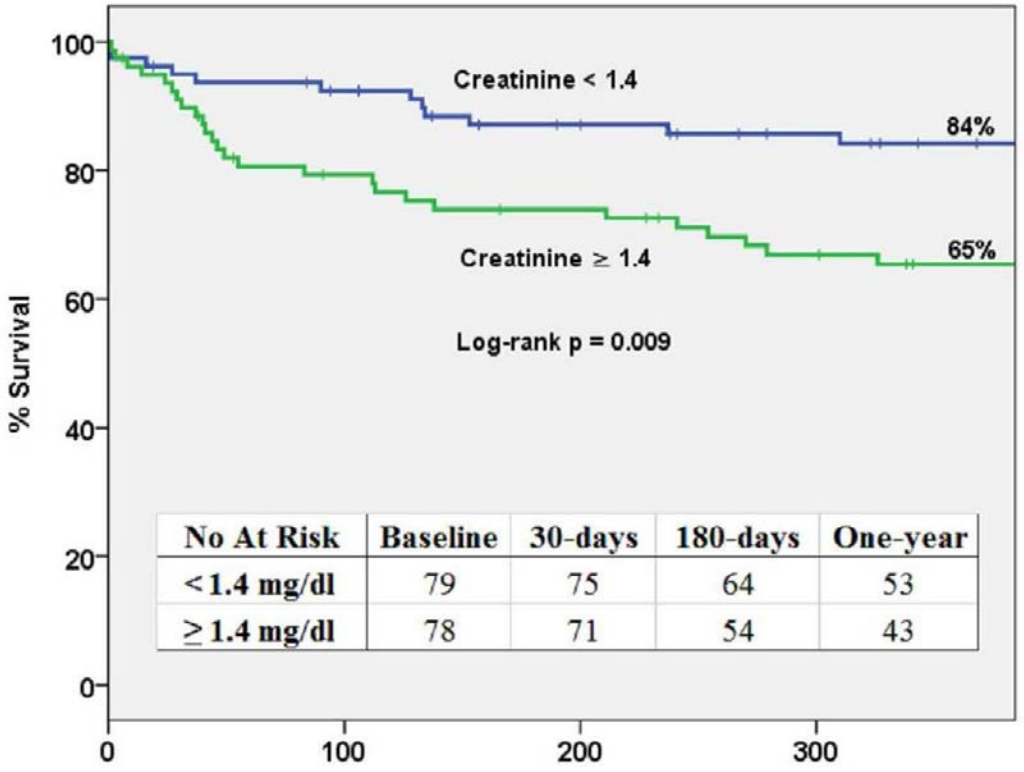
Survival



Kim et al J. Card Failure 2016

Survival post-LVAD

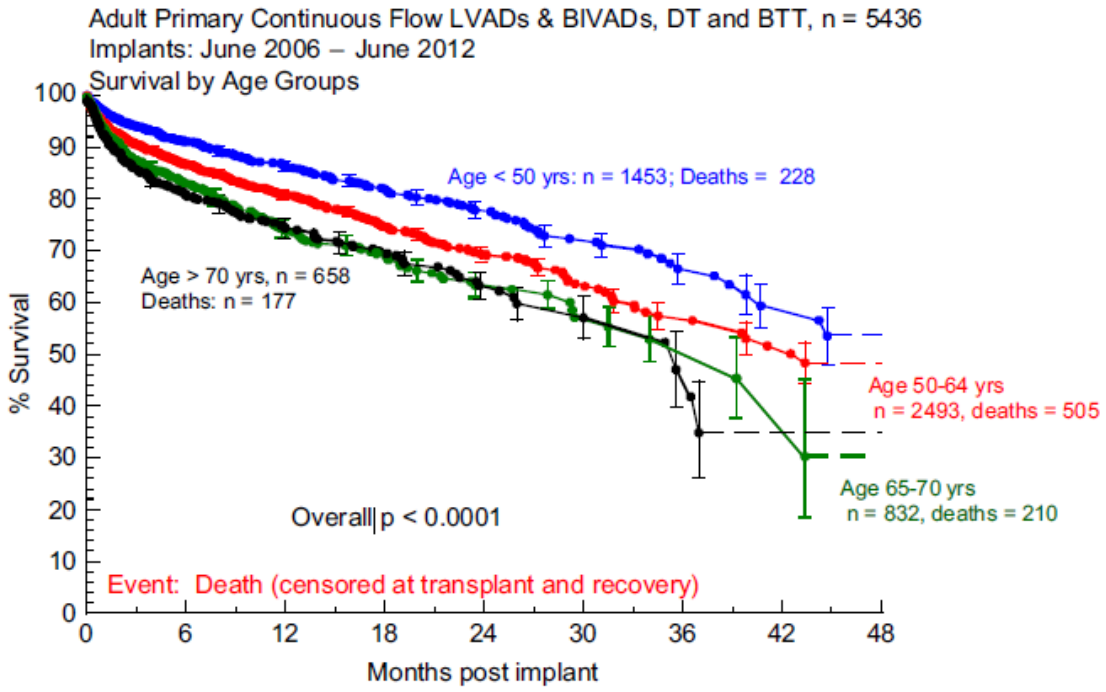
- Advanced age as a dichotomized variable around age 70 is not a significant independent predictor of survival
- When age is set as a continuous variable – predicts mortality with a 20% increase risk of death/10 years of life.
- Known that age is a strong predictor of GIB – age >65 associated with a 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



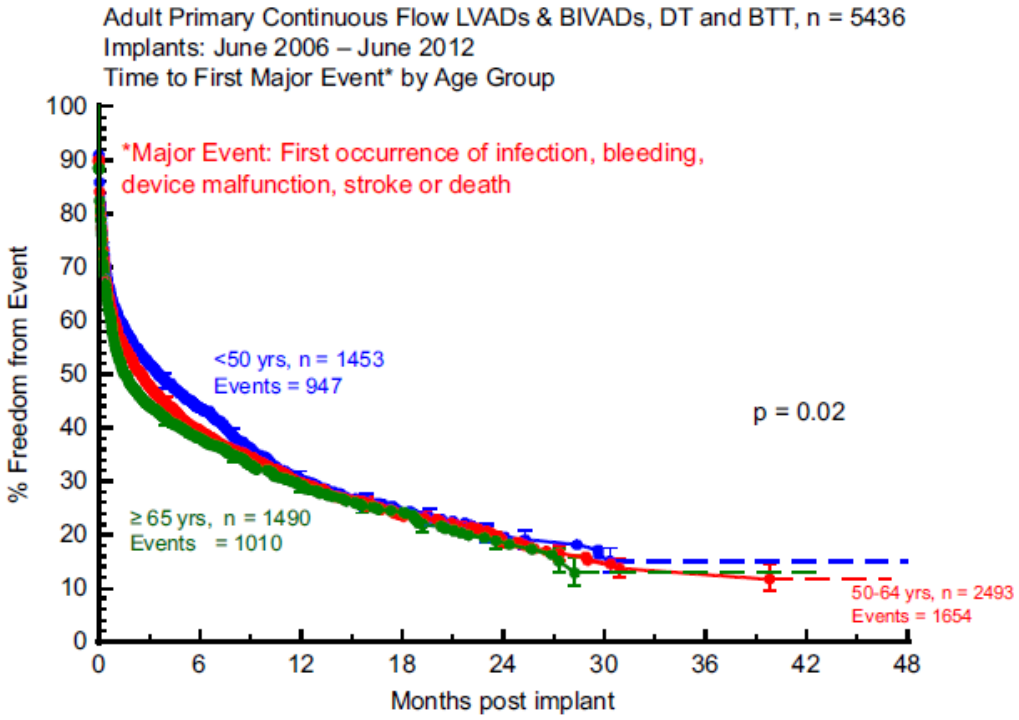
No At Risk	Baseline	30-days	180-days	One-year
< 1.4 mg/dl	79	75	64	53
≥ 1.4 mg/dl	78	71	54	43

Kim et al J. Card Failure 2016

Age as an independent risk factor for death among LVAD recipients



Freedom from adverse events after LVAD stratified by age



Kirklin et al., JHLT 2013

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Heart Failure

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

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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: ≥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

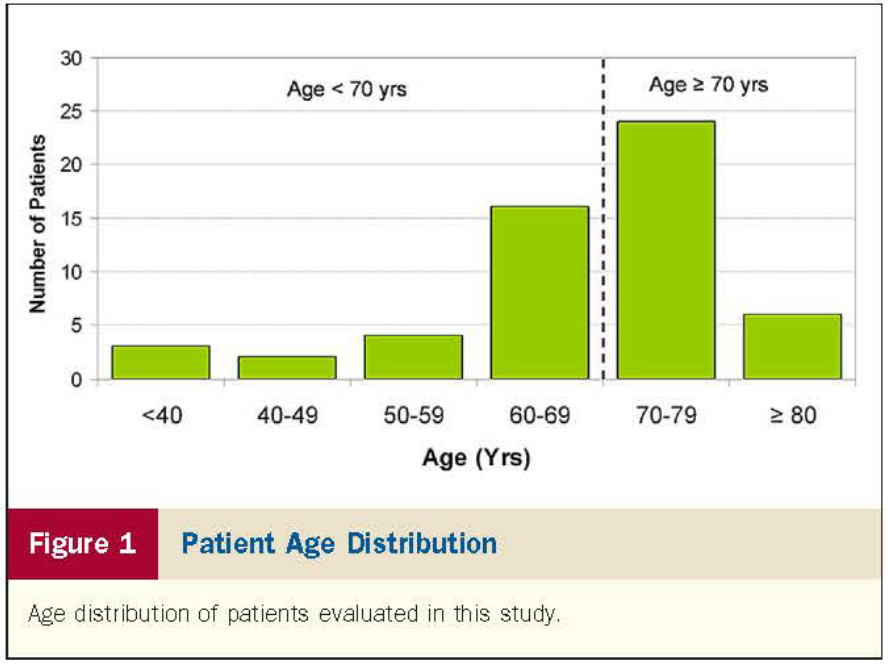


Figure 1 **Patient Age Distribution**

Age distribution of patients evaluated in this study.

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

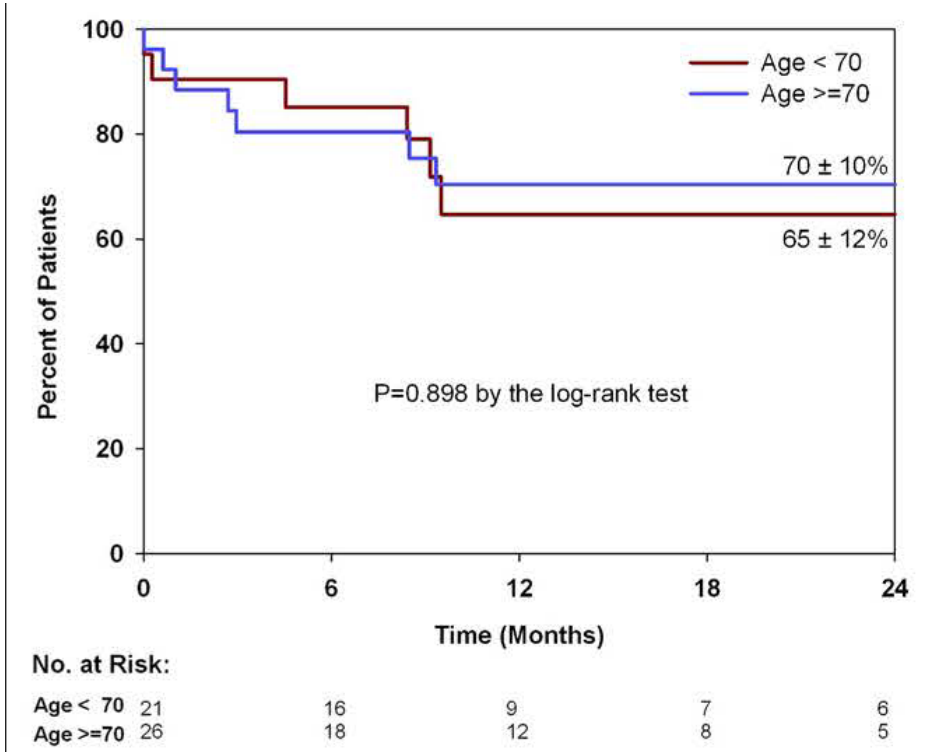


Figure 2 **Kaplan-Meier Survival Analysis**

Adamsom et al., JACC 2011

Pre-operative risk factors for outcomes

Boyle et al 2014

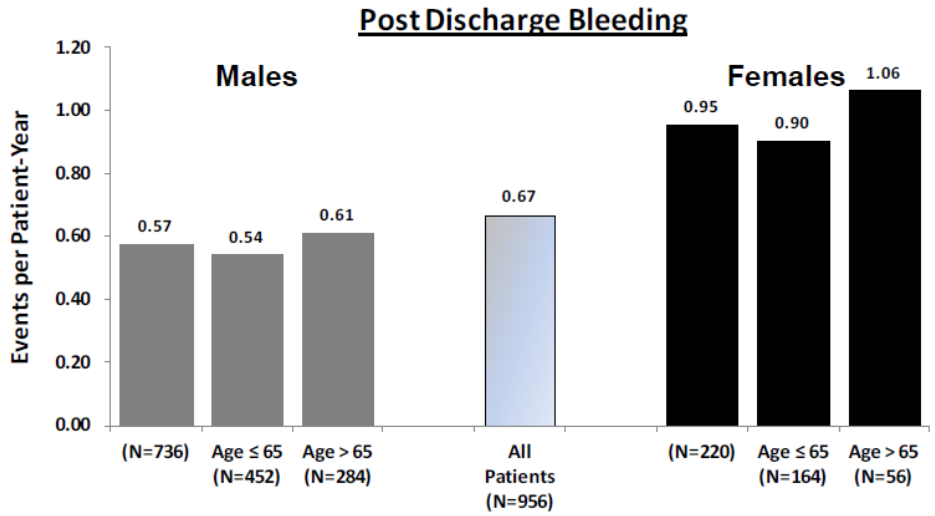
- Retrospective
- Patients with HMII as part of DT or BTT clinical trials
  - 2005 – 2010
  - 1,302 patients (956 patients included in the analysis)
  - 2 years follow-up

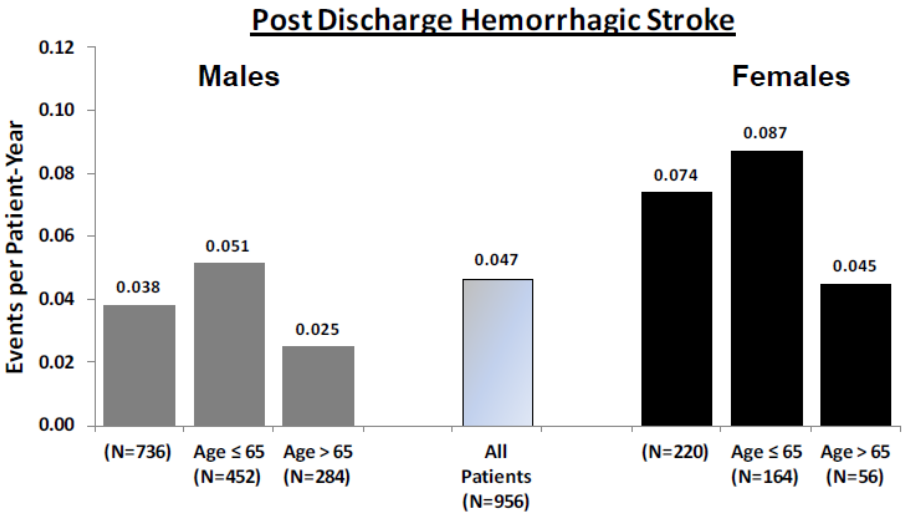
Effects of Gender and Age

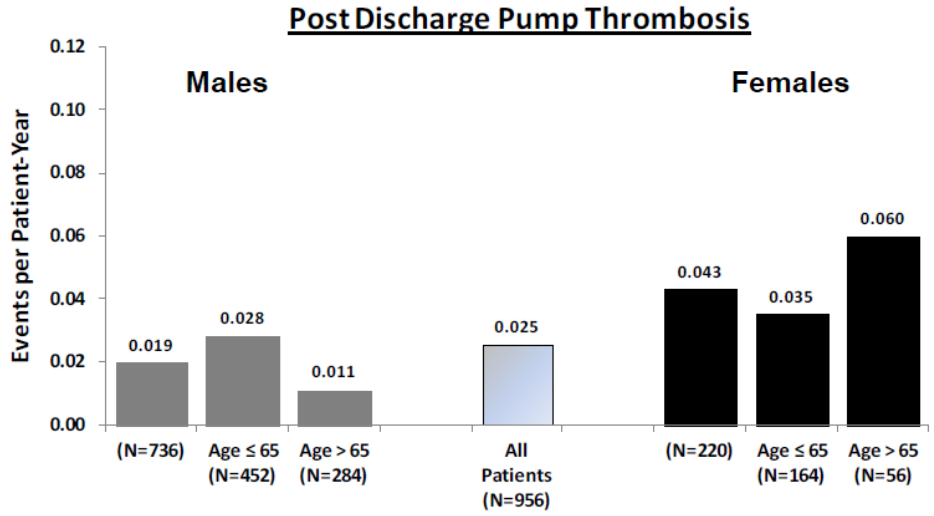
Older age, and its associated risk of GIB has been well documented.

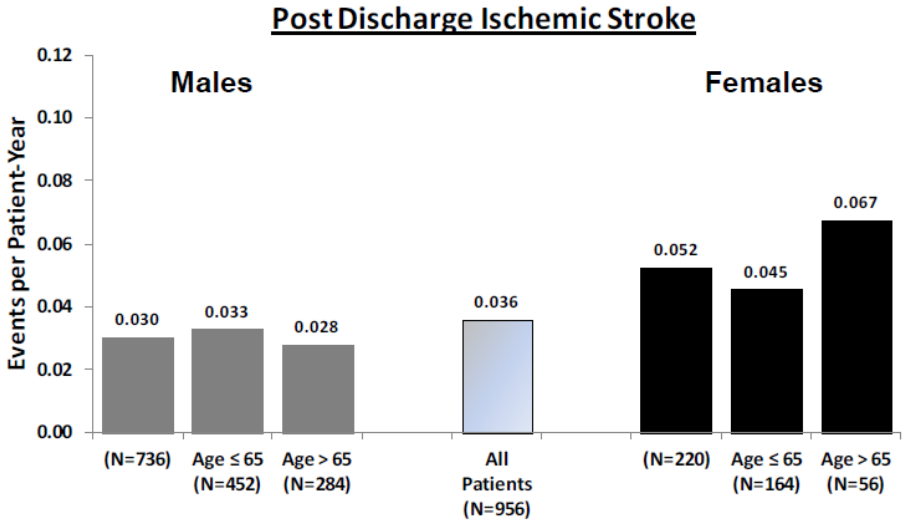
This analysis showed older patients were at a higher risk of:

- bleeding events
- female gender
- anemia before surgery
- risk of stroke (females)









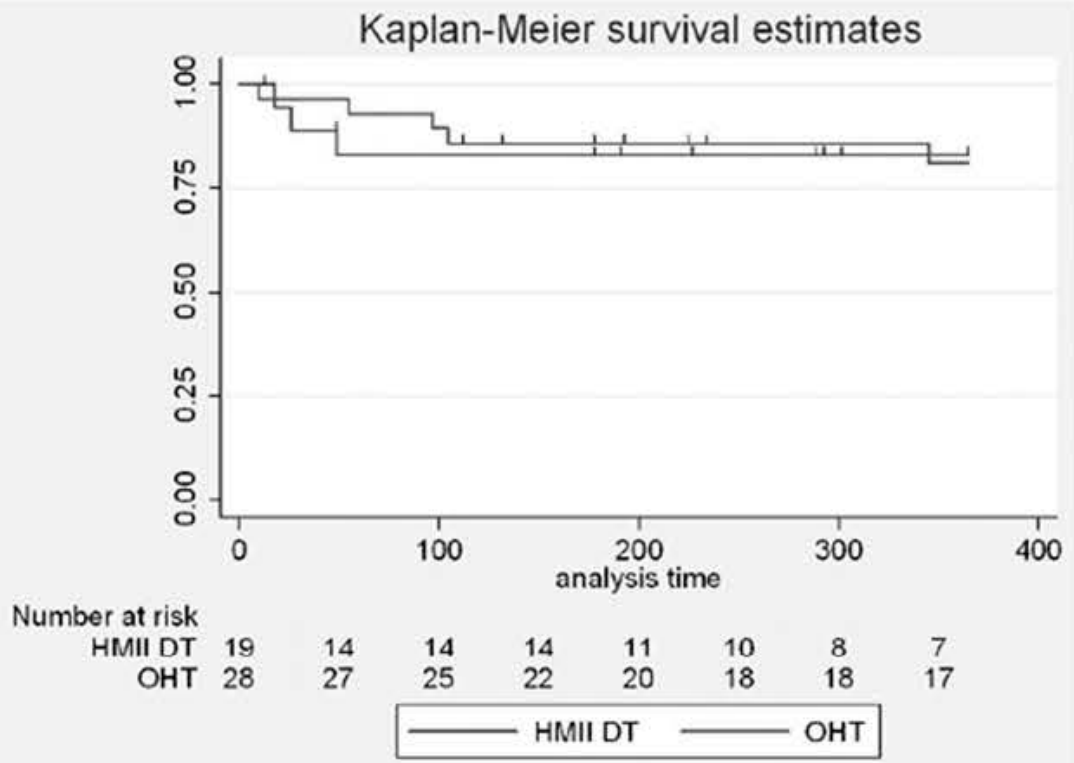
Boyle et al, JACC 2014

LVAD vs Transplant

LVAD vs OHT

Single centre – Columbia

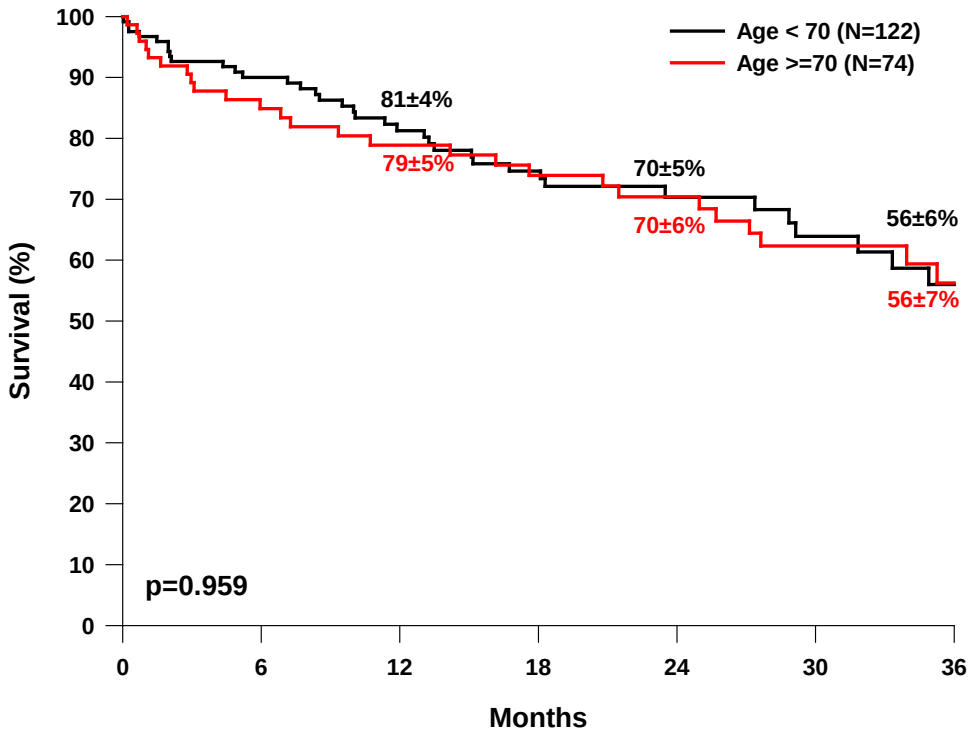
- 19 LVAD vs 28 OHT
- LVAD patients were older (72yo vs 68 yo)
- 1year survival similar
- LVAD group had a longer ICU and total length of stay

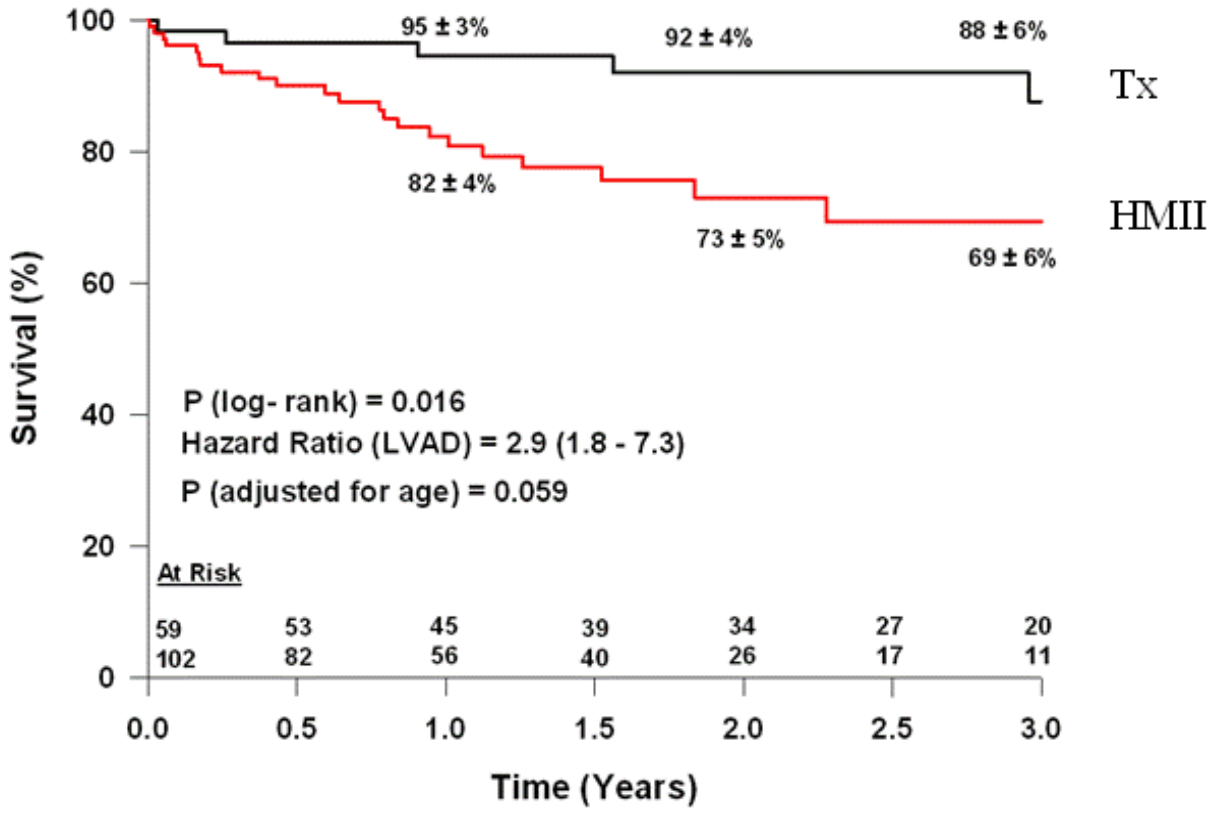


Conclusions: Survival rates during the first year following surgery in LVAD patients are excellent and comparable to those seen in OHT recipients older than 65 years of age at our institution. Postoperative ICU stay and total postoperative stay were significantly longer in the LVAD group.

Abstract - Melnitchouk et al., JHLT 2011

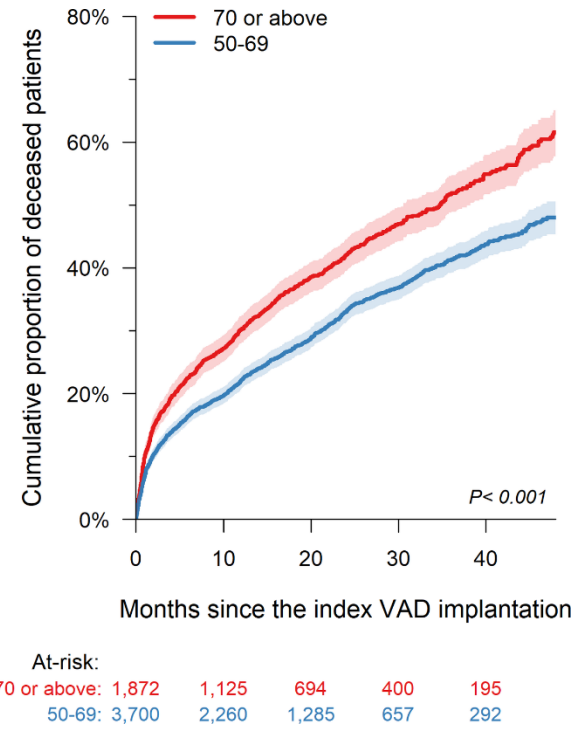
Survival: HeartMate II vs Transplant



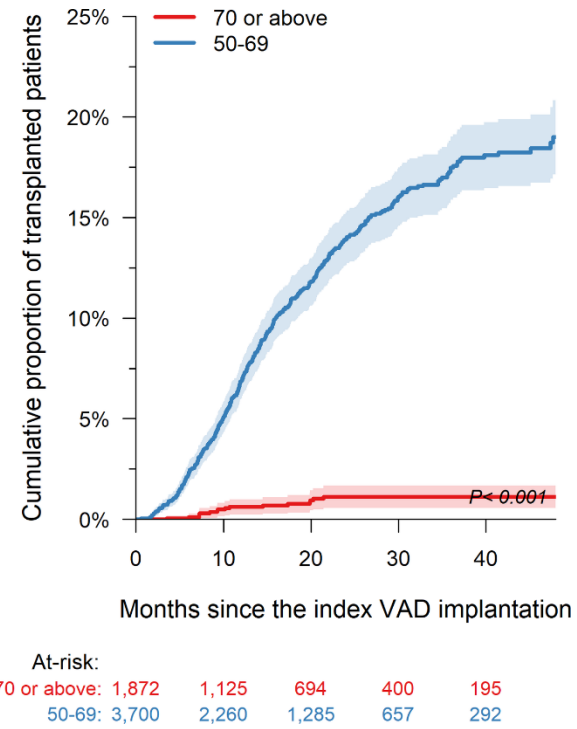


Adamson et al., 2011; unpublished

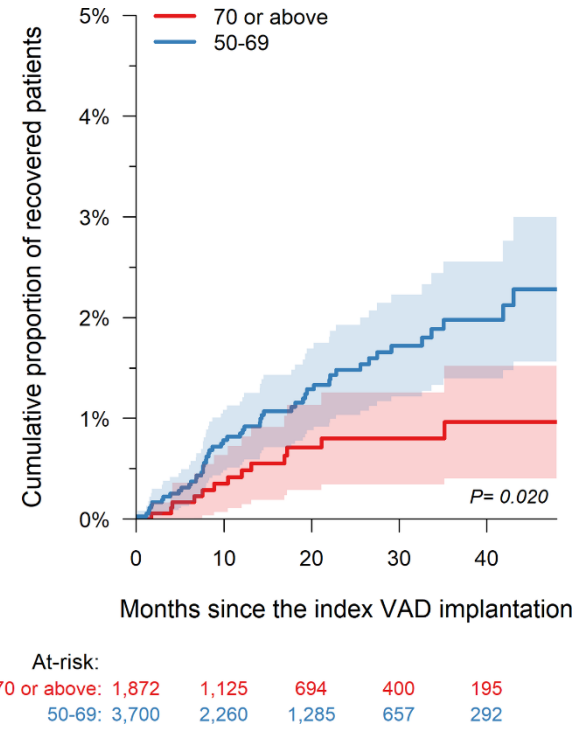
INTERMACs – Cumulative incidence



post-VAD mortality



post-VAD transplantation

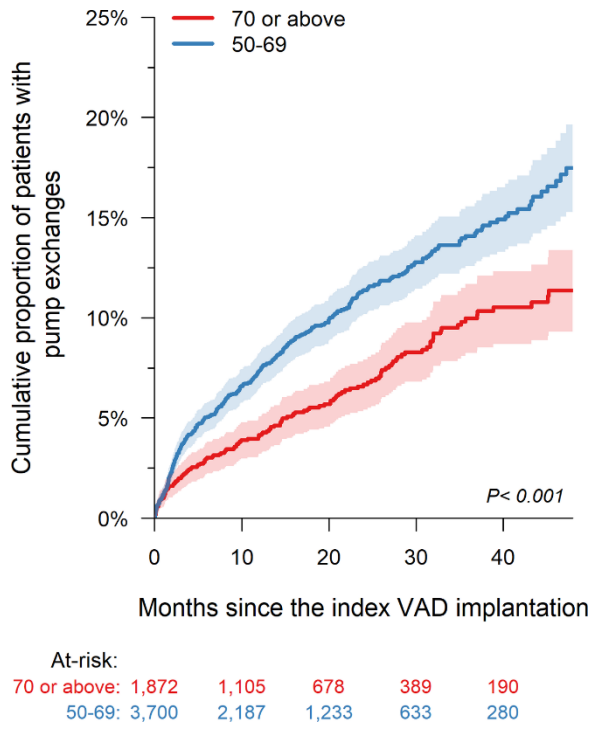


post-VAD recovery

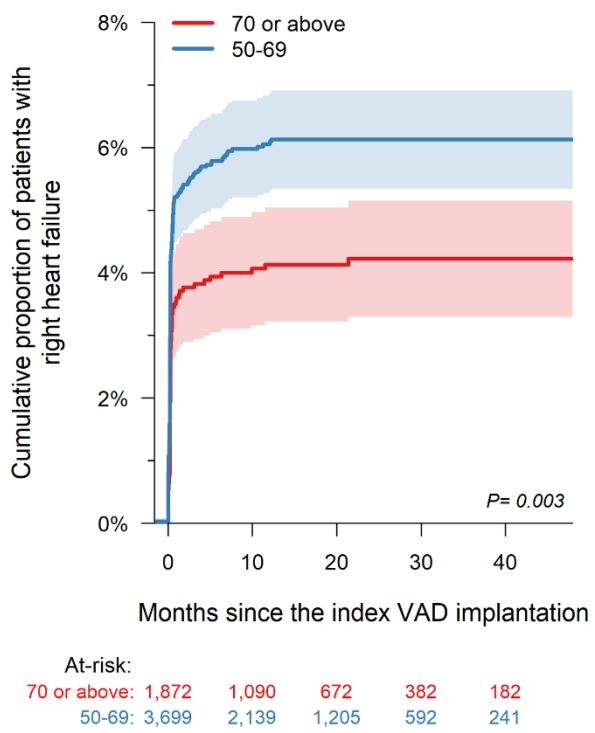
Aleksova et al, unpublished data 2019

Complications post-VAD

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



Pump exchange



Right heart failure

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?

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