

"Stage D Heart Failure" - When to Consider Advanced HF Rx
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 Chulalongkorn University

2017 HFCT Annual Scientific Meeting
 16.6.2017



5 treatments options for stage D HF



OPTIONS:

1. Heart transplant
2. Ventricular assist device
3. Chronic home inotrope
4. Palliative care
5. Investigational surgery or medications

DEPEND ON:

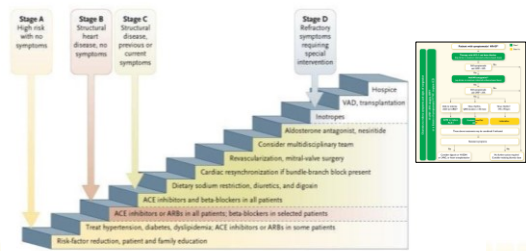
1. Patient goal of living
2. Transplant candidacy
3. How much time left ?

Complimenting rather than in insolation

5% of HF population are stage D HF



First, you have to do EVERYTHING that you can ... but non of them seem to work



Jessup M, Brozena S. N Engl J Med 2003;348:2007-2018.

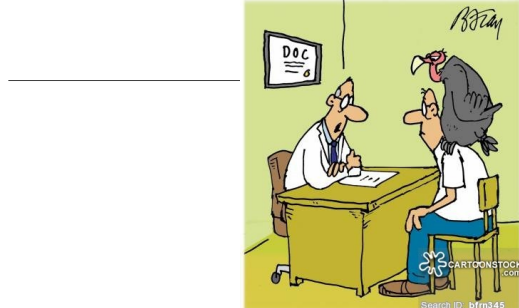
5% of HF population are stage D HF



- "Refractory symptoms of HF, despite GDM"
 - Dyspnea at rest or minimal activities
 - Frequent/prolong hospitalization
 - Cardiac cachexia, CKD, PH, cirrhosis
- High mortality and morbidity
 - 20-50% survival at 1 year
- Can be either inpatient or outpatient
 - Some are "inotrope dependent"



You know when you see it



Signs that death is near → referral center

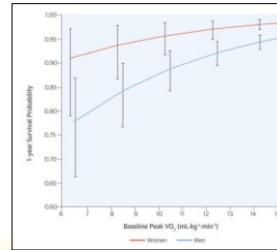


- NYHA III-IV
- 6WMT < 350
- persistent of congestion
- Recurrent HF hosp.
- Recurrent VT, ICD shock
- Not a CRT candidate
- Cannot tolerate BB/ACEI/MRA
- Less responsive to diuretics

- Age, BMI, HR, SBP
 - EF, Cr, Na, Alb, Hb
 - QRS width, LV size
 - BNP, troponin
 - peak VO2
- Risk model
- HFSS: Circ 1997;95:2660-7.
 - SHFM: Circ 2006;113(11):1424.

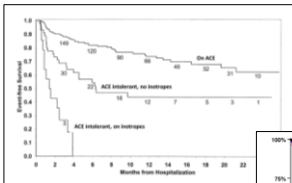
ESC 2012 HF guideline. Eur H J 2012;33:1787-847

Peak VO2 and 1-year survival



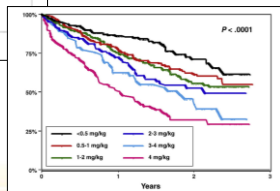
HF-ACTION JACC 2016

Intolerance of ACEI



JACC 2003;41:2029-35

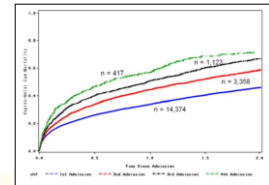
Unresponsive to diuretics



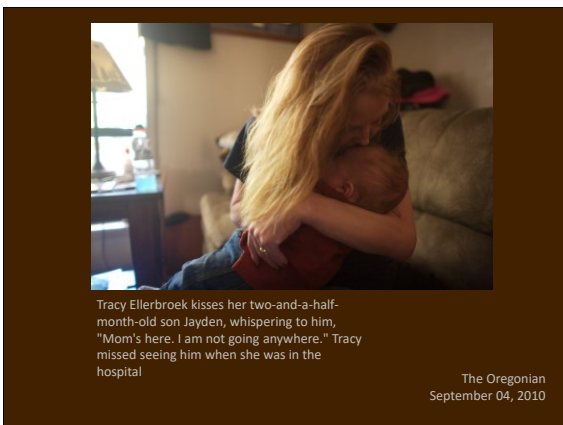
PRAISE-1 NEJM 1996

Repeated hospitalizations predict mortality in the community population with heart failure

- 14,374 pts from admin registry of British Columbia
- Median survival after the HF hospitalization
 - 1st = 2.4 yr
 - 2nd = 1.4 yr
 - 3rd = 1.0 yr
 - 4th = 0.6 yr

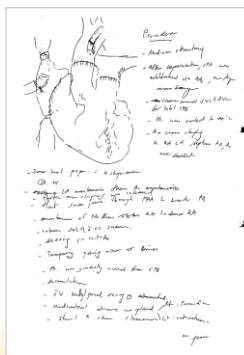


HF-ACTION JACC 2016



Tracy Ellerbroek kisses her two-and-a-half-month-old son Jayden, whispering to him, "Mom's here. I am not going anywhere." Tracy missed seeing him when she was in the hospital

The Oregonian
September 04, 2010



Heart transplant is the best option for survival and QoL

- Durable
- Biventricular support
- Biocompatible

Thailand: 20/yr

Heart Transplant in Asia

Rungroj Kittiyaphong, MD, FCCP, FCCM, AHA/ACC/AHA/ASA, ACCP, ACC

KEYWORDS
Heart transplant • Asia • Heart failure

KEY POINTS

In Asia the heart transplant program began in Taiwan and Thailand in 1987. At present, there are at least 10 Asian countries that have experience in heart transplant operations. However, the number of heart transplants, mainly due to the implementation of legislation for organ donation. The underlying heart disease for heart transplant recipients was predominantly coronary artery disease followed by ischemic cardiomyopathy, similar to reports from Western countries. However, valvular heart disease was more common in Asia. Survival at 1, 5, and 10 years after heart transplant in Asia was similar to that in Western countries.



Fig. 1. Number of heart transplants in each Asian country by year.

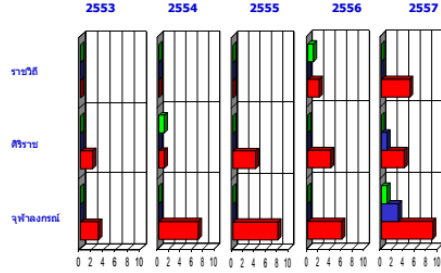


Heart Failure Clin 2015;11:563-572.



Cardiac Center
Heart Failure and Transplant

แผนภูมิแสดงจำนวนการปลูกถ่ายหัวใจ หัวใจและปอด ปลูก ตั้งแต่ 1 มกราคม 2553 - 31 ธันวาคม 2557 จำนวนตามโรงพยาบาล



Cardiac Center
Heart Failure and Transplant

ศูนย์รับบริจาคอวัยวะสภากาชาดไทย รายงานประจำปี 2557

Very selected patient will benefit from HTx

Table 2. Contraindications to HT

Relative contraindications
 Systemic illness with a life expectancy < 2 y despite HT, including:
 Active or recent acute organ or blood malignancy within 5 y (eg, leukemia, low-grade lymphoma) or prostate with potentially limited curable-specific therapy
 AIDS with frequent opportunistic infections
 Systemic bone metastases, central, or metastases that are malignant involvement and is still active
 Intractable renal or hepatic dysfunction or patient considered for only HT
 Significant obstructive pulmonary disease (FEV₁ < 1 L/min)
Fixed pulmonary hypertension
 Pulmonary artery systolic pressure > 40 mm Hg
 Mean transpulmonary gradient > 15 mm Hg
 Pulmonary vascular resistance > 4 Wood units

Absolute contraindications
 Age > 75 y
 Any acute infection with exception of sterile-related infection in VAD recipient
 Active major organ disease
 Severe diabetic mellitus with end-organ damage (nephropathy, retinopathy, or neuropathy)
 Severe peripheral vascular or cerebrovascular disease
 Hospital-acquired infection not amenable to surgical or pharmacologic therapy
 Congenitally aortic disease
 Aortic bicuspid aorta < 3.7
 Unresected abdominal aortic aneurysm > 4 cm
 Single-chamber study mean value > 20 ng/ml or aortic study mean value < 18 ng/ml*
 Cholesterol < 153 mg/dL, or combined cholesterol < 254 mg/dL*
 Blood urea > 23 mg/dL, serum transaminase > 5×, BUN < 3.0 off dialysis
 Severe pulmonary infection with FEV₁ < 60% normal
 Recent pulmonary infection within 6 to 8 wk
 Difficult to control hypertension
 Intractable neurological or neuromuscular disorder
 Active mental illness or psychiatric instability
 Drug, tobacco, or alcohol abuse within 6 mo
 Recent reduced thrombocytopenia within 100 d
 HT recipient unresected common bile duct
 *May be suitable for HT if metabolic support and hematologic management possible in candidate < 15 mg/dL, and combined cholesterol < 254 mg/dL
 Transplantation may also be suitable in candidate heart failure transplantation



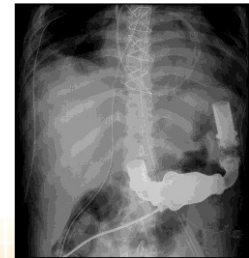
Cardiac Center
Heart Failure and Transplant

Selection of Cardiac Transplantation Candidates. Mancini D. Circ 2010;122:173-183.

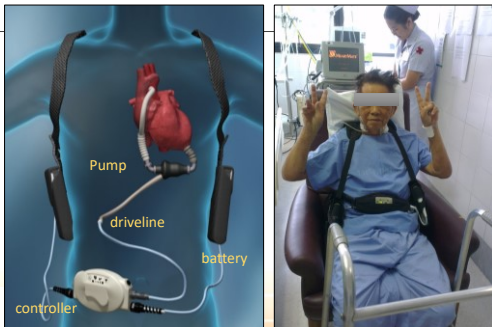
Heart mate III



Heart mate II



HeartMate II VAD (Thoratec)



Indications for MCS

- Bridge to transplant (BTT)
- Destination therapy (DT)
- Bridge to ...
 - To recovery:
 - Shock, post cardiac surgery, post MI, myocarditis
 - To decision:
 - Evaluation for OHT candidacy status
 - Perioperative:
 - High risk PCI, percutaneous valve, ablation.

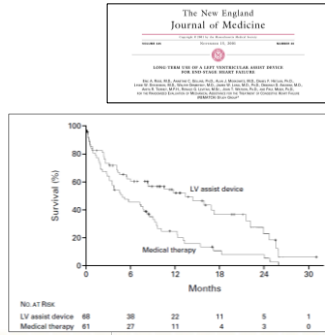


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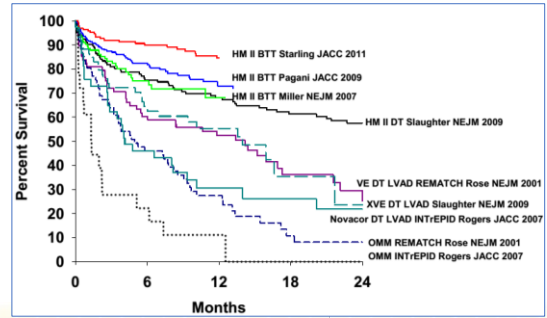
Circulation. 2012;126:2648-2667.

REMATCH study

- HF stage D and not a transplant candidates
- 129 pts
- Pulsatile flow LVAD vs. OMM
- LVAD resulted in a survival benefit



NEJM 2001; 345:1435-43.

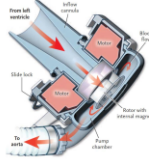


Fang JC. NEJM 2009;361:2282.

Ongoing technology

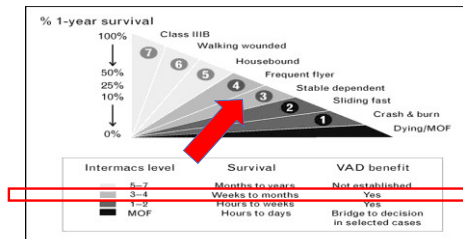
LVAD Technology Evolves

THE NEW ENGLAND JOURNAL OF MEDICINE
ORIGINAL ARTICLE
A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure
Hemerson P. Vavala, M.D., Nicholas Iliadis, M.D., No-Ulani M.D., Daniel J. Goldstein, M.D., Joseph C. Cleveland, Jr., M.D., Paul C. Colombo, M.D., Wiley W. Webb, M.D., Cameron D. Murray, M.D., Christen B. Park, M.D., Ulrich P. Jorde, M.D., Franco D. Pagani, M.D., Keith D. Anderson, M.D., Donald E. Saxon, M.D., Kelly McCune, M.D., Alexander Hink, M.D., Gregory A. Ewald, M.D., Douglas Thumranontakul, M.D., James W. Long, M.D., and Christopher Salerno, M.D., for the MAGLEVAD Investigators*



N ENGL J MED 376:5 NEJM.ORG FEBRUARY 2, 2017

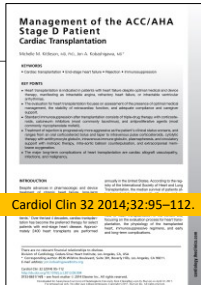
Too soon or too late



The figure illustrates seven INTERMACS levels of clinical severity of end-stage heart failure with the corresponding survival. The time frame for consideration of mechanical circulatory support and evidence from clinical trials of 1-year survival benefit with LVAD implantation is shown in the table.

	Heart Transplant	Mechanical Circulatory Support
Indication	Gold standard Improve survival + QoL	BTT, DT, decision Improve survival + QoL
1-yr survival	85 - 90%	70-80%
Limitation	Limit candidacy Limited donors Very selected patient	Financially restrict Unmatured technology Very selected patient
Experiences	- Worldwide: 4000 / year - Thailand: 20 / year	> 5,000 / year 5 patients total
A Disease by itself	Immunosuppressant Endomyocardial biopsy "New kind of patient"	Anticoagulation Wound dressing "New kind of patient" – no pulse
Complications	Rejection Infection Malignance	RV failure Bleed/ Clot Infection





Cardiol Clin 32 2014;32:95-112.



J Am Coll Cardiol 2015;65:2542-55.

Recommendation for Advanced Rx

Recommendations	COR	LOE	References
MCS			
MCS is beneficial in carefully selected* patients with stage D HF in whom definitive management (eg, cardiac transplantation) is anticipated or planned	IIa	B	660-667
Nondurable MCS is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected* patients with HF and acute profound disease	IIa	B	668-671
Durable MCS is reasonable to prolong survival for carefully selected* patients with stage D HF.††	IIa	B	672-675
Cardiac transplantation			
Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management	I	C	680

ACC 2013

Recommendation for Advanced Rx

Recommendations	COR	LOE	References
Inotropic support	I	C	N/A
Chronotropic block pending definitive therapy or resolution	IIa	B	647, 648
BTT or MCS in stage D refractory to GDMT	IIIb	B	592, 649, 650
Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HF.††	IIIb	B	651-653
Long-term support with continuous infusion palliative therapy in select stage D HF	IIIb	B	651-653
Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF	III. Harm	B	416, 654-659
Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful	III. Harm	B	592, 649, 650
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ACC 2013

Long term home inotrope

- Use of inotrope is controversial but common
 - 75% in OMM arm of REMATCH
- Chronic, ambulatory home inotropic infusion
 - ↑ CO by ↑ contractility
- Agents
 - Dopamine
 - Dobutamine
 - Milrinone
- Recently available in Thailand

NEJM 2001

Limited evidences

- Safe
 - Improve hemodynamics by RHC
 - Allow death at home
 - Decreased hospitalization
 - ? Effect on mortality
 - Cost saving
- 2 groups of patients -
 - "A bridge" - Awaiting HTx or MCS -
 - Palliative care

Circ Heart Fail. 2015;8:880-886.
Am J of Hospice & Palliative Medi 2013;29(4): 249-253.
Am Heart J. 2006;6:1096.e1-8

	Inotropes Use in Previous Era		Inotropes Use in Current Era	
	Herzbarger et al ¹¹	Herzogen et al ¹²	Gorodetski et al ¹³	Hashim et al ¹⁴
Inotrope used	Dobutamine or milrinone	Dobutamine or milrinone	50% dobutamine, 50% milrinone	15% dobutamine, 85% milrinone
Dose of inotrope	Dobutamine: 6.8 ± 3.4 µg/kg/min Milrinone: 0.6 ± 0.3 µg/kg/min	Not reported	± 2.5 µg/kg/min Milrinone: 0.8 ± 0.2 µg/kg/min	Dobutamine: ± 4.4 µg/kg/min Milrinone: 0.8 ± 0.3 µg/kg/min
History of prior ventricular tachycardia (%)	Not reported	Not reported	Not reported	30
Prevalence of defibrillators (%)	14	Not reported	65	84
Use of neurohormonal antagonists while on inotropes				
β-blockers (%)	Not reported	19	19	72
Angiotensin-converting enzyme inhibitors (%)	69	36	40	50
Angiotensin receptor blocker (%)	2	9.60	5	13
Allosteric antagonists (%)	Not reported	Not reported	44-59	59
Median survival	3.4 mo	3-6 mo	9-18 mo	18 mo (9 mo for patients on inotropes only for palliation)
6-mo survival (%)	26	57	45	60
1-yr survival (%)	8	43	50	68
Survival according to inotrope used	Not reported	Not reported	No significant difference in adjusted mortality	Milrinone better than dobutamine (P<.01)
Hospitalizations after inotrope initiated	Equivalent pre- and postinotrope	Reduced	Reduced	Reduced

Heart Failure Clin 2016;12:437

Original Article
Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure
 Simonon-Hadley, MD, Kumar-Saxena, MD, Maron-Rovillo-Mattar, MD, Chandy J. Morgan, PhD, Ince A. Saha, MD, Saha V. Panamburam, MD, MPhI, Ramo Y. Luyago-Rendon, MD, PhD, James P. George, PhD, Deepak Acharya, MD, MPhI

- 197 patients on home inotrope
 - 54 yo, EF 20% 40% ischemic
 - 84% milrinone
- Mean F/U 3 - 12.2 mo
 - 36% death, 25% still on inotrope, 12% wean off inotrope, 12% MCS, 16% HTx
- 55/60 successfully bridge

Table 2. Initial Follow-Up and Hospitalizations on Inotropes

	Death (n=63)	Weaned (n=26)	Remained on Inotropes (n=52)	Transplant (n=23)	LVD (n=32)
Time between initiation of inotropes and either clinical visit (d, median [IQR])	26 (3-108), n=52	38 (3-225), n=23	34 (3-214), n=48	19 (5-798), n=21	17 (5-378), n=27
No. of hospitalizations on inotropes	1.8 (2.1)	1.2 (1.5)	1.9 (1.9)	0.7 (1.6)	0.9 (1.1)
Follow-up time on inotropes	6.5 (7.6)	19.2 (8.8)	12.2 (11.5)	3.8 (8.3)	3.0 (2.7)

IQR indicates interquartile range; and LVD, left ventricular assist device.



Circ Heart Fail. 2015;8:880-886.

COSI STUDY

Clinical Investigation
Care Process and Clinical Outcomes of Continuous Inpatient Support With Inotropes (COSI) in Patients With Refractory Endstage Heart Failure
 Patel J, Hernandez-Sol, Garcia-Gonzalez, RN, Shah A, Nataraj, MD, Glickson, RN, Jovin, MD, PhD

- 36 inotrope-dependent patients, not a Htx candidate
 - 55.4 yo, EF 20%, LVEDDD 70 mm
 - ICD = 5
 - Mostly dobutamine
- Median survival = 3.4 months
- 55% death at home

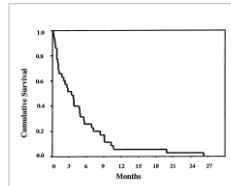


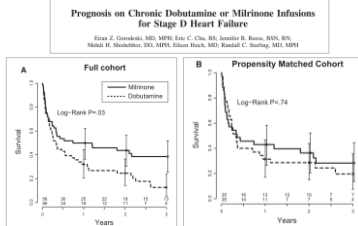
Fig. 1. The probability of survival is plotted over time; 3-, 6-, and 12-month survivals were 51%, 26%, and 6%, respectively. One subject who underwent aortic valve replacement after 2.4 months of COSI has not been included in this analysis.



J of Cardiac Fail 2003;9:180-187.

No mortality differences between dobutamine and milrinone

- Retrospective
- 112 inotrope-dependent stage D HF not HTx candidates
- Mean dose:
 - Dobutamine (5.4 mcg/kg/min)
 - Milrinone (0.4 mcg/kg/min)



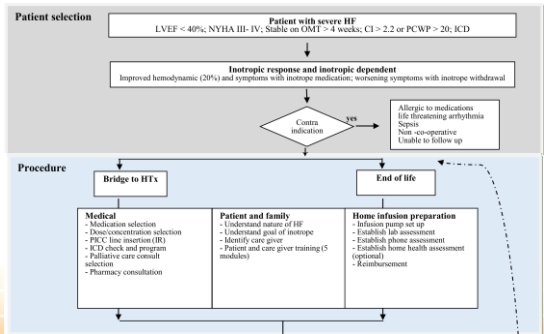
Circ Heart Fail. 2009;2:320-324.

Milrinone

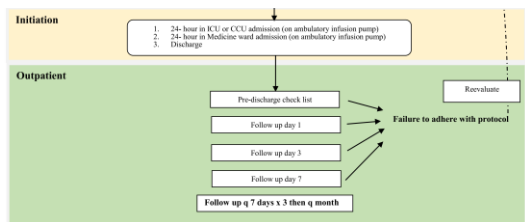
- Phosphodiesterase 3 inhibition
 - Increased cyclic AMP
 - Can be co-administer with BBs
- Effect
 - ↑ contractility, ↑ CO, ↓ PCWP
 - ↑ systemic vasodilation
 - ↑ pulmonary vasodilator, ↓ PA
- Typical dose: 0.125 - 0.75 µg/kg/min
- Long duration
 - T1/2 = 2.5 hours
 - Excreted by renal,
- Side effect: Hypotension, AT, VT



How we do it



How we do it



Ambulatory infusion pump

- Battery > 24 hours
- Small, light weight, lock screen



Inotrope Summary

- Home inotropes are safe
 - for both bridge to HTx, MCS or destination Rx
- Recently data suggests improved 1 year mortality
 - Reduce Hospitalizations
 - Improved QoL
- Need extensive patient education and discussion



Recommendation for Advanced Rx

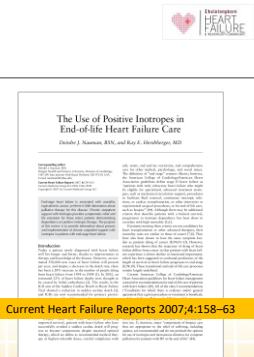
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ACC 2013

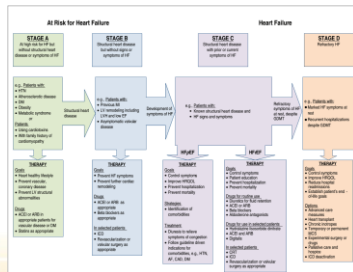


Circ Heart Fail 2015;8:880-6.

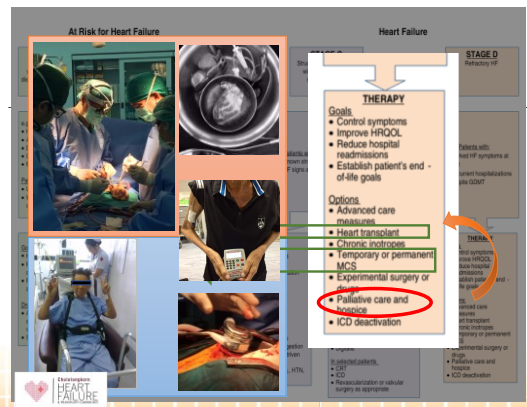


Current Heart Failure Reports 2007;4:158-63

ACC/AHA HF guideline 2013



Yancy CW. ACC/AHA HF guideline. Circ 2013;128:e240-e327



Yancy CW. ACC/AHA HF guideline. Circ 2013;128:e240-e327

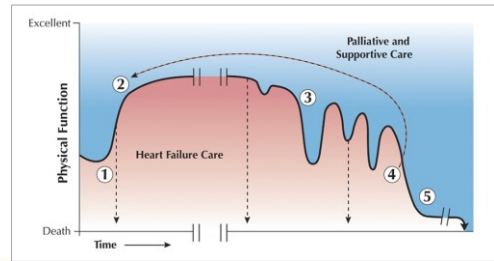
Palliative care

- “patient and family-centered care that optimizes QOL by anticipating, preventing, and treating suffering”
- Appropriate at any age and at any stage in a serious illness
 - Palliative care ≠ end of life care

Clinical Practice Guidelines for Quality Palliative Care, 2013

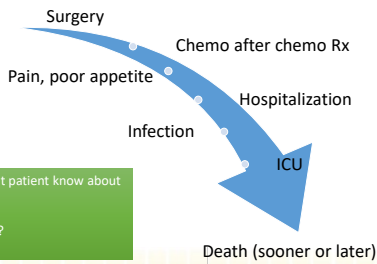


Heart Failure Disease Progression



Goodlin SJ. JACC 2009;54:386–96.

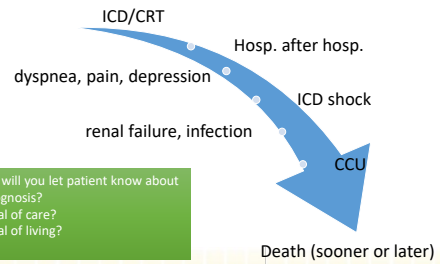
Colon Cancer stage III



When will you let patient know about

- Prognosis?
- Goal of care?
- Goal of living?

Stage D HF (20% mortality at 1 year)



When will you let patient know about

- Prognosis?
- Goal of care?
- Goal of living?

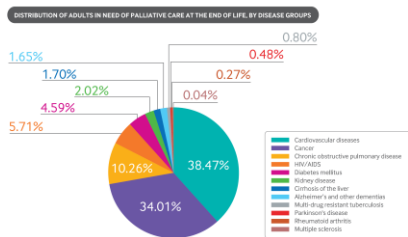
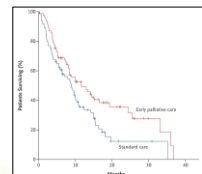
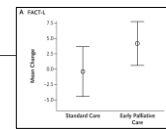


Fig 11 Distribution of adults in need of palliative care at the end of life by disease. *Adapted, with permission, from the World Health Organization¹⁸.



ORIGINAL ARTICLE
 Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer
 Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alexa Musickanday, M.A.

- RCT, n= 151
- Metastatic non-small-cell lung cancer
- Palliative care on top standard care
- Result
 - Despite less aggressive care
 - Better QoL, depression
 - 2.7 month survival benefits



N Engl J Med 2010;363:733–42.



Limited evidence in HF patients

Sidebottom A, et al. *J Palliat Med* 2015;18:134-42.

- RCT, 232 patients AHF (usual vs. usual + PC)
- Equal survival, 30-day re-hosp.
- Improve QOL, symptoms (dyspnea, pain, tiredness, depression, anxiety), advance care plan

ACC/AHA 2013

Class I, LoE B

Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life.^{30,385-388} (Level of Evidence: B)

The prognosis of patients hospitalized with HF, and especially those with serial readmissions, is suboptimal. Hence, appropriate levels of symptomatic relief, support, and palliative care for patients with chronic HF should be addressed as an ongoing key component of the plan of care, especially when patients are hospitalized with acute decompensation.³⁸⁶

- My idea
- VAD/HTx discussion
 - All stage D
 - ICD implant/ upgrade
 - Why not everyone

Challenge

Zimmerman C, et al., *Can Med Assn J*, 2016

- "Stigma of death, hopelessness, dependency, comfort care"
- "Palliative care = the person's on death row"
- "Take you off medication and just comfort care"

Dunlay SM, et al. *Pall Med*, 2015

- Provider discomfort (11%)
- Perception of patient/ family unreadiness (21 + 12%)
- Fear of destroying hope (9%)
- Lack of time (8%)
- Lack of confidence (>30%)

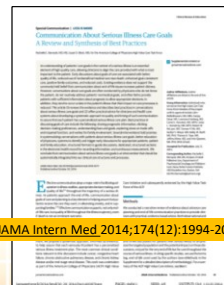


My thoughts

- Variable prognosis
- Episodic improvement in symptoms
- **The easiest option is not making any decision**

Hospice care – End of life care

- When curative treatments are no longer beneficial
- When the burdens of treatments exceed the benefits
- When patients are entering the last weeks of life
- ≠ euthanasia or physician assist suicide



Thank you

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