(Advanced) Heart Failure Pharmacology

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Outline

- Tips/Pearls for the use and optimization of our "standard trio" (ACEI/BB/Diuretic) used in chronic heart failure
- Second/third line therapies and how to use them, including newer agents
- Diuretic resistance
- Questions and hopefully answers

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ACE Inhibitors: Considerations for Use

- Maximize dose until not tolerated
  - BP as a commodity in HF, not a target
- Elevated *chronic* serum creatinine is not a contraindication - may see up to 20% increase with initiation or dose increase
- To be initiated in all patients with significantly reduced LVEF unless contraindicated
- To be used indefinitely

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Why ACEI's are Important: CONSENSUS

- Enalapril in patients with NYHA IV HF
- NNT (number needed to treat) of **5** to prevent 1 death at 6 months

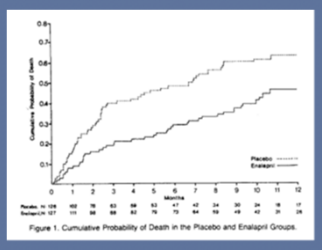

Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.

N Engl J Med. 1987;316:1429-35

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ACEIs and ARBs: Considerations for Changing Therapy

- Is it truly an ACE inhibitor cough?
  - consider fluid, optimize diuretic dose
- Are there reasons not to consider an ARB?
  - Hypotension, hyperkalemia, renal dysfunction
- Are there reasons to consider an ARB?
  - Intolerable cough, angioedema (caution)
- Combination ACEI and ARB therapy
  - Reduction in morbidity (HF hospitalizations), no impact in mortality
  - Consider when symptomatic despite target ACEI and ARB dose

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ACE Inhibitors – Alternatives Summary

- Angiotensin-II receptor Blockers (ARBs)
  - Use if cough with ACE-inhibitor
  - Consider if angioedema with ACE-inhibitor (caution)
  - Additive (ACEI + ARB) afterload reduction if max ACEI (reduces HF hospitalizations)
- Isosorbide dinitrate + hydralazine
  - Use as alternative to ACEI/ARB
  - Decreases mortality compared to placebo
    - Less effective than ACEI
  - Use in addition to ACEI/ARB if African American pt

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Aldosterone Inhibitor Pearls

- Contraindications
  - Hyperkalemia > 5.5 mmol/L
  - Renal Insufficiency, SCr > 2.5 mg/dL
- Monitor serum potassium at frequent intervals
  - Recommend K check within a week of discharge and monthly x 3 months
- Start ACE-I/ARB first
- Consider modifying or discontinuing K supplement
- Reduce dose if hyperkalemia develops
  - K^+ > 5.5 mmol/L → Reduce to 12.5 mg daily
  - K^+ low → Consider 50mg daily

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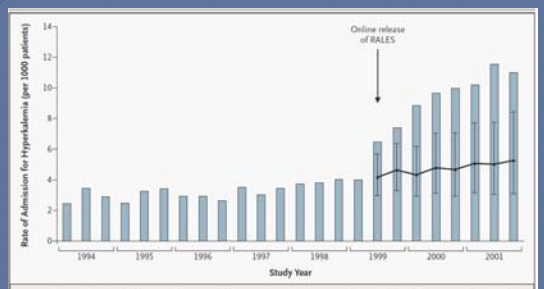

Figure 2. Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of hospital admission for hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected admission rates for hyperkalemia derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Juurlink DN, et al. N Engl J Med 2004; 351:543-551

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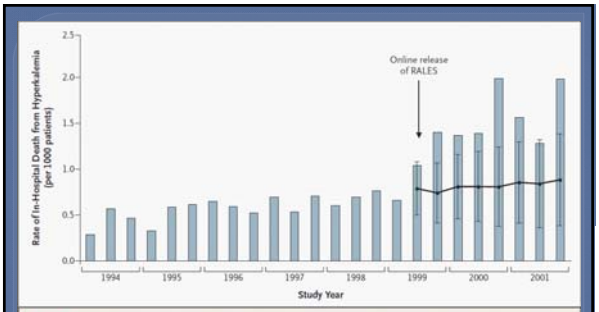

Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Juurlink DN, et al. N Engl J Med 2004; 351:543-551

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Beta-Blocker Pearls

- Start on hemodynamically stable patients
- ↑ To target dose
  - Go slowly
  - Usually no more then every 2-4 weeks as outpatient
  - May have to increase diuretic to increase BB
  - Improvement is dose-dependent
- Watch for side effects

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Digoxin Pearls

- Use as 4th line therapy in pts who remain symptomatic on diuretic, ACEI and BB
- Dual cardiac mechanisms:
  - Positive inotropic effect due to inhibition of Na/K/ATPase channel resulting in preferential use of Na/Ca channel, increasing intramyocitic calcium concentration
  - Increase in parasympathetic activity via vagal nerve stimulation
  - Compensatory neurohormonal action – decreased norepinephrine
    - Slows heart rate
- "Feel Good Drug"
- Watch for changes in renal function or potassium
- Drug Interactions:
  - Amiodarone increases PO digoxin absorption (P-glycoprotein inhibition) – drop digoxin dose by 50%

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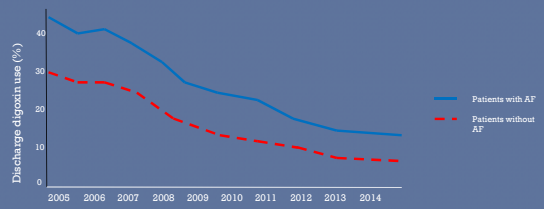
Digoxin Use is Declining



J Am Coll Cardiol HF 2016;4:348–56

New Therapies for Chronic Heart Failure

- Angiotensin Receptor Neprilysin Inhibitor (ARNI):
  - Valsartan/Sacubitril (LCZ696, Entresto®)
- Ivabradine (Corlanor®)
  - Recent FDA approval – patients with systolic heart failure (EF ≤ 35%) in NSR on maximal tolerated beta blocker with HR ≥ 70 or contraindicated for beta-blocker

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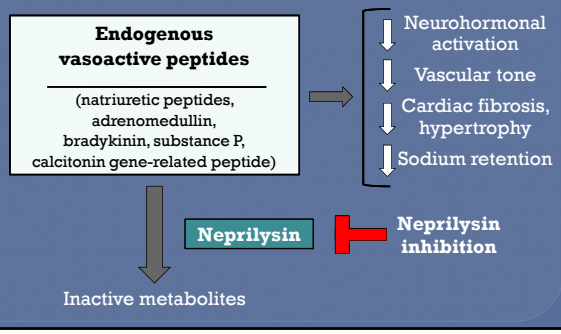
Neprilysin Inhibition

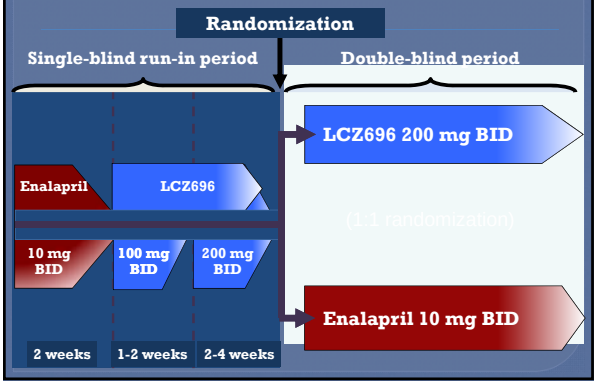


PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40% → 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg twice daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m^2 and serum K ≤ 5.4 mEq/L at randomization

N Engl J Med 2014; 371:993-1004

PARADIGM-HF: Study Design



PARADIGM-HF: Endpoints

	LCZ696 (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	p value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71- 0.89)	0.00004

N Engl J Med 2014; 371:993-1004

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	p value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

N Engl J Med 2014; 371:993-1004

PIONEER

- N=881, randomized double-blind, active control
- Inclusion: LVEF <40% + elevated BNP with ADHF diagnosis, SBP at least 100 mm Hg, stable diuretic dose, no inotropes within 24 hours
- Patients enrolled between 24h and 10 days after admission while in hospital
- Primary endpoint: change in NT-proBNP from baseline to week 4 and 8

N Engl J Med. 2019 Feb 7;380(6):539-548.

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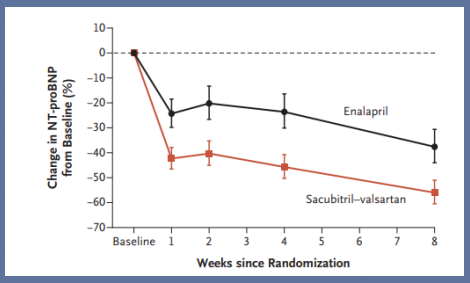
PIONEER



N Engl J Med. 2019 Feb 7;380(6):539-548.

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PIONEER

	Sacubitril-Valsartan (n=440)	Enalapril (n=441)	Hazard Ratio or Relative Risk (95% CI)
Exploratory Clinical Outcomes – n (%)			
Death	10 (2.3)	15 (3.4)	0.66 (0.30-1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37-0.84)
Key Safety Outcomes – n (%)			
Worsening renal function	60 (13.6)	65 (14.7)	0.93 (0.67-1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84-1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85-1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02-1.38)

N Engl J Med. 2019 Feb 7;380(6):539-548.

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PARAGON-HF

- N=4822, randomized, double-blind, active controlled to sacubitril-valsartan or valsartan
- Inclusion: NYHA II-IV symptoms, age > 50, EF ≥ 45%, elevated BNP, evidence of structural heart disease
- Primary endpoint: composite of HF hospitalizations or death from CV causes

N Engl J Med. 2019 Oct 24;381(17):1609-1620

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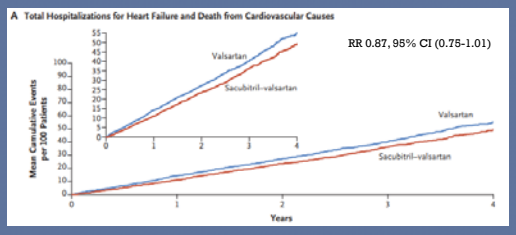
PARAGON-HF



N Engl J Med. 2019 Oct 24;381(17):1609-1620

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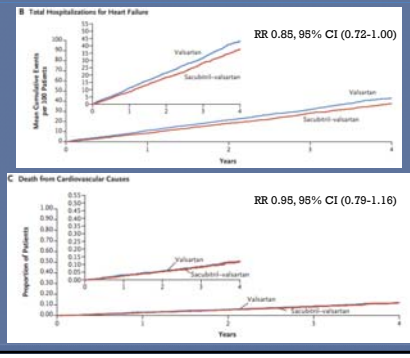
PARAGON-HF



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PARAGON-HF

Table 3. Adverse Events during Randomized Treatment.

Event	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	P Value
Hypotension with systolic blood pressure <100 mm Hg — no. (%)	380 (15.8)	257 (10.8)	<0.001
Elevated serum creatinine — no. (%)			
≥2.0 mg/dl	261 (10.8)	328 (13.7)	0.002
≥2.5 mg/dl	97 (4.0)	109 (4.6)	0.36
≥3.0 mg/dl	38 (1.6)	40 (1.7)	0.79
Elevated serum potassium — no./total no. (%)			
>5.5 mmol/liter	316/2386 (13.2)	361/2367 (15.3)	0.048
>6.0 mmol/liter	75/2386 (3.1)	101/2367 (4.3)	0.04
Angioedema — no. (%)	14 (0.6)	4 (0.2)	0.02
Liver-related adverse event — no. (%)	151 (6.3)	178 (7.5)	0.11

N Engl J Med. 2019 Oct 24;381(17):1609-1620

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Sacubitril-Valsartan

Final Thoughts

- ACEIs (and ARBs) are still first-line therapy for patients with heart failure
- We should consider converting people on maximum tolerated baseline HF therapy (including ACEI/ARB) when persistently symptomatic or admitted with ADHF
- Cost (and insurance barriers) are an issue
- Overall no role in HFpEF – some subgroups may benefit

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Ivabradine (Corolan®)

- Binds to the I_f channel
  - Reduces slope for diastolic depolarization, prolonging diastolic duration
  - Does not alter ventricular repolarization, myocardial contractility, or BP
- Bind to the F channel in the open position – greatest effect when HR highest
- Contraindications:
  - HR < 60, BP < 90/50, ADHF, sick sinus syndrome, Class II or complete AVB, hepatic dysfx, pregnancy/breast feeding

SHIFT Trial

Systolic Heart failure treatment with the I_F inhibitor ivabradine Trial

Prospective, randomized, double-blind, placebo controlled trial

n = 6,558
HF, LVEF ≤ 35%, HR ≥ 70 bpm, NSR, and previous admission for worsening HF within the prior 12 months

Ivabradine 5 mg BID* | Placebo

Primary endpoint: CV death or admission for worsening HF

*Titrated at 14 days based upon heart rate

The Lancet 2010; 376:875-885

SHIFT Trial: Primary Endpoint

Outcomes	IVA (%) (n=3241)	PLB (%) (n=3264)	HR (95% CI)	p value
CV death or HF hospitalization	24	29	0.82 (0.75–0.90)	<0.0001
HF death	3	5	0.74 (0.58–0.94)	0.014
HF hospitalization	16	21	0.74 (0.66–0.83)	<0.0001
CV death, HF hospitalization, or admission for nonfatal MI	25	30	0.82 (0.74-0.89)	<0.0001

The Lancet 2010; 376:875-885

Selected Adverse Events

	Ivabradine N=3232, n (%)	Placebo N=3260, n (%)	*p* value
All serious adverse events	**1450** (45%)	**1553** (48%)	**0.025**
All adverse events	2439 (75%)	2423 (74%)	0.303
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012
Phosphenes	89 (3%)	17 (1%)	<0.0001
Blurred vision	17 (1%)	7 (<1%)	0.042

The Lancet 2010; 376:875-885

Chronic Heart Failure

Upcoming Changes in Care

- Ivabradine re-emphasizes the role of HR as a treatment target
  - Relatively complex patient-selection
  - Unique adverse effect profile
  - Some potential to increase AF
- Valsartan/Sacubitril
  - ADE's (greater than ACEI/ARB): hypotension, angioedema
    - Label contraindication: do not administer to patients who have received ACEI within 36 hours (angioedema) or in patients receiving aliskiren
  - Limitations: suboptimal ACEI comparison (enalapril 10 mg bid); what about that ACEI vs. ARB trial?
  - Will we "tier" heart failure therapy (again) based on access to care?

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Ivabradine vs. Digoxin

- Digoxin is no longer first-line therapy in patients with heart failure
  - Digoxin use should likely be relegated to specialized HF or EP clinics
- Digoxin may be useful as secondary therapy in patients with continued symptoms or intolerant/contraindicated for first-line therapy (especially beta-blockers)
  - Ivabradine may be a better choice but potentially unaffordable for many
- Digoxin still has a role in heart failure patients with atrial fibrillation
  - Ivabradine may slow rate in AF due to more widespread If activity than previously thought
  - Ivabradine also may cause AF
- Other cardiac indications:
  - Congenital
  - RV inotropic support (patients with LVADs, pulmonary hypertension)

Diuretic Pearls

- Dosing
  - Loop diuretics as first-line in CHF
  - Diuretic sliding scale
- Monitor
  - Daily weights
  - Fluid intake, urine output, creatinine clearance
  - Dizziness, lethargy, blood pressure
  - Shortness of breath, dyspnea, chest xray
  - Ankle edema
  - Muscle cramping (bumetanide > furosemide), electrolytes

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Intravenous Loop Diuretics

- Loop diuretics are generally equal in efficacy if given in equipotent doses (IV)
  - Furosemide 40 mg
  - Torsemide 10-20 mg
  - Bumetanide 1 mg
- Ethacrynic acid (no sulfonamide moiety)
- Loop diuretics and gout

Expert Opin Pharmacother. 2013 Aug;14(12):1641-8

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Diuretic Response

- In general, targeting 2-3L fluid removal per day
- Outpatient:
  - Increasing oral doses of furosemide (usually outpatient)
  - Change to oral bumetanide or torsemide
    - Furosemide F (bioavailability)= 0.1-1 (0.5 average)
    - Bumetanide F= 0.8-1
  - Synergistic blockade (thiazide + loop) (caution!)
- Inpatient:
  - Switch to IVP furosemide once hospitalized
  - Give larger IV doses or more frequently if some response
  - Continuous IV infusions
    - Furosemide up to 40-80 mg/hr, Bumetanide 1-2 mg/hr
  - Synergistic blockade (thiazide + loop)
    - Check electrolytes q12h
  - Ultrafiltration

Expert Opin Pharmacother. 2013 Aug;14(12):1641-8

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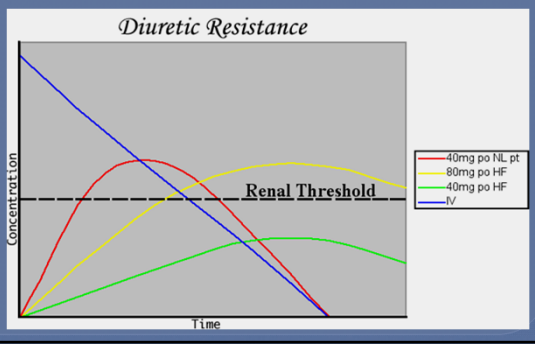
Furosemide in Heart Failure



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Thiazides

- Used in combination with loop diuretics
  - Synergistic diuresis due to adaptive sodium reabsorption in the distal tubule
- All thiazides are generally equal in efficacy if given in equipotent doses
  - Hydrochlorothiazide 25-50mg PO daily
  - Metolazone 2.5-5mg PO daily
  - Chlorothiazide 250-500mg IV Q12h
- Give 30 minutes prior to loop diuretic
  - Not that important with metolazone due to long half-life
- Efficacy significantly decreased with CrCl < 30ml/min
- Can cause profound diuresis and electrolyte depletion
  - Be VERY cautious using as outpatient
  - Consider increasing electrolyte replacement regimen
  - Not desirable for continuous use – best as a "pulse"

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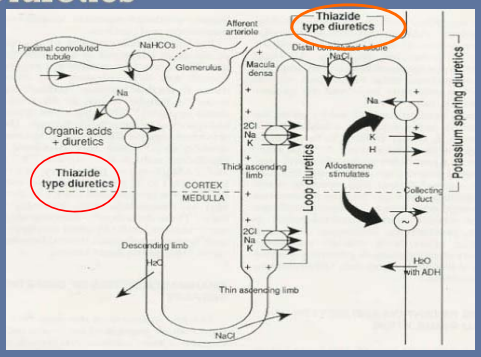
Diuretics



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Diuretics Summary

- Evaluate and treat diuretic resistance
- If loop alone is inadequate add a thiazide for synergistic effect
- Add K^+-sparing to conserve K^+ or treat symptoms
- Goal is to relieve congestive symptoms
- Diuretics do not reduce mortality in HF patients

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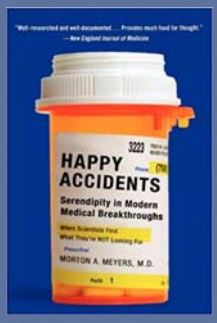

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SGLT-2 Inhibitors in HF

- Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have been approved for a number of years for the treatment of type 2 diabetes
  - "-Flozin" drugs – canagliflozin, dapagliflozin, empagliflozin
- Reductions in the new incidence of HF have been consistently identified in clinical trials examining cardiovascular outcomes with SGLT-2 inhibitors
  - Important since some diabetes may worsen HF and are contraindicated (pioglitazone, rosiglitazone)

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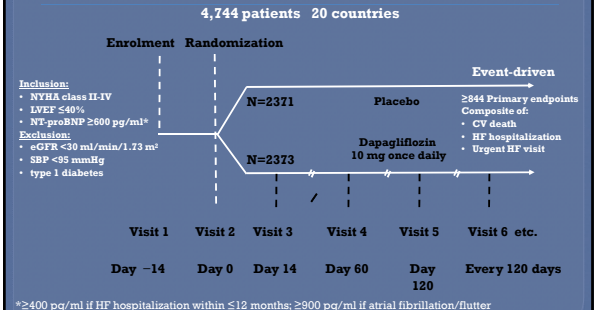
DAPA-HF Design



*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

N Engl J Med. 2019 Nov 21;381(21):1995-2008.

DAPA-HF

Characteristic	Diabetes (n=2139)*	No diabetes (n=2605)
Mean age (yr)	67	66
Male (%)	78	76
NYHA class II/III/IV (%)	**64/35/1**	**71/29/1**
Mean LVEF (%)	31	31
Median NT-proBNP (pg/ml)	1484	1413
Mean systolic BP (mmHg)	123	121
Ischaemic aetiology (%)	**62**	**51**
Mean eGFR (ml/min/1.73m²)	63	68
eGFR <60 ml/min/1.73m² (%)	**46**	**36**
Prior heart failure hospitalization (%)	49	46

N Engl J Med. 2019 Nov 21;381(21):1995-2008. 43

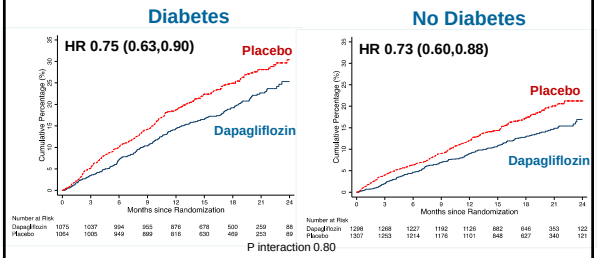
DAPA-HF

Treatment (%)	Diabetes (n=2139)	No diabetes (n=2605)
Diuretic	95	92
ACE-inhibitor/ARB/ARNI⁺	93	94
ACE inhibitor	55	57
ARB	29	27
Sacubitril/valsartan	11	11
Beta-blocker	97	96
MRA	72	71
ICD*	27	26
CRT**	7	8

N Engl J Med. 2019 Nov 21;381(21):1995-2008. 44

Primary composite outcome

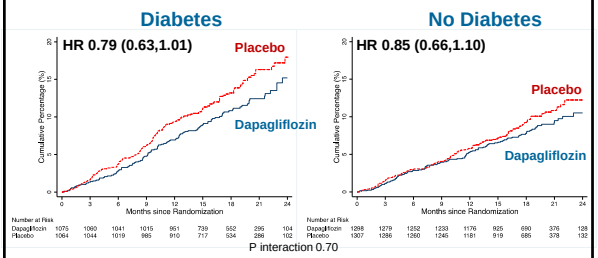
CV Death/HF hospitalization/Urgent HF visit



P interaction 0.80

Components of primary outcome

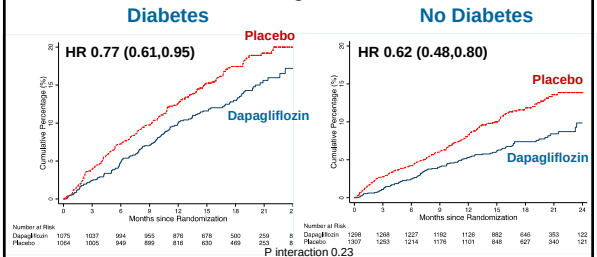
Cardiovascular death



P interaction 0.70

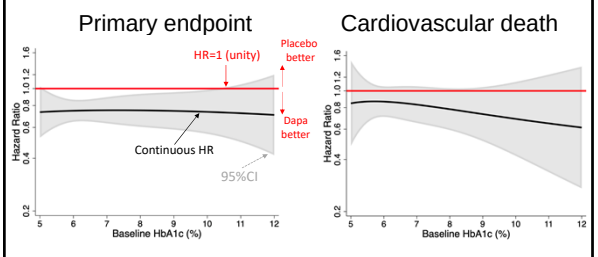
Components of primary outcome

Worsening HF event



P interaction 0.23

Treatment effect according to baseline HbA1c (All patients)



SGLT-2s in HF

- Mechanism: ?
  - Increased diuretic/natriuretic effect
  - Off-target benefit direct to myocardium/vascular system
- Under fast track approval by the FDA currently for expanded indication
- ACC/AHA/HFSA guidelines have not addressed
  - Likely to be a Class I recommendation in patients symptomatic despite maximally tolerated therapy
  - Very strong evidence SGLT-2 should be first line for patient with HF and type 2 diabetes
- Expensive

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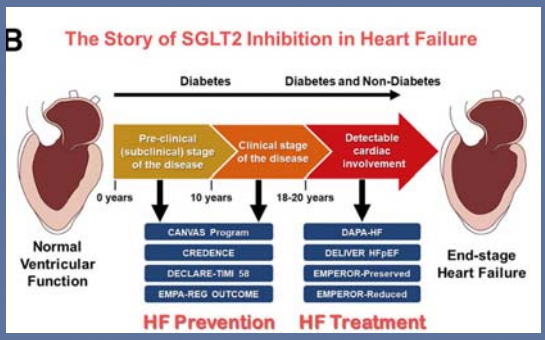

Bhatt DL, et al. Cell Metab. 2019 Nov 5;30(5):847-849

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Agents on the Horizon

Therapy	Mechanism of Action
~~Serelaxin~~	Recombinant human relaxin 2, modulates CV response during pregnancy (RELAX-AHF-2 missed primary endpoint)
~~Ularitide~~	Atrial natriuretic peptide (urodilatin); vasodilator, diuretic (TRUE-AHF trial negative)
Anakinra	IL-1 receptor antagonist (anti-inflammatory)
Omecamtiv mecarbil	Cardiac-specific activator of myosin, improves myocardial efficiency
~~Aliskiren~~	Direct renin inhibitor with favorable neurohormonal and hemodynamic effects (ATMOSPHERE negative)
Nitroxyl donors	Reduced form of NO with arterial and venodilatory properties and inotropic and lusitropic properties
Cenderitide (CD-NP)	Chimeric protein which causes cGMP-mediated venodilation and aldosterone blockade
~~Cinaciguat~~, Vericiguat	Vasodilator that activates soluble guanylyl cyclase, leading to increased cGMP and venous and arterial vasodilation
Clevidipine	Calcium channel blocker that selectively dilates arteries with no significant effect on myocardial contractility
Istaroxime	Inhibits sodium-potassium ATP activity and stimulates SERCA2a, thereby increasing lusitropy and inotropy

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Questions?

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Updates in the Transplant Allocation System

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Disclosures

None

Outline

- History of the heart transplant allocation system
- Why change?
- The new allocation system
- Evaluating the new system

History of Donor Heart Allocation

"The scarcity of organs, the growing need for this life-saving therapy, and changes in technology have made creating and maintaining the allocation system challenging and, at times, faced with medical and ethical dilemmas."

J Hoosain and S Hankins. Curr Cardiol Rep (2019) 21: 67

Organ Procurement and Transplantation Network: The Final Rule

- "Allocation policies shall be designed to achieve equitable allocation of organs among patients"
- "Setting priority rankings expressed … through objective and measurable medical criteria … These rankings shall be ordered from most to least medically urgent … There shall be a sufficient number of categories … to avoid grouping together patients with substantially different medical urgency"
- "Distributing organs over as broad a geographic area as feasible"

History of the allocation system

- Primary factors taken into account
  - Acuity of illness
  - Time spent waiting on the list
  - Blood type compatibility
  - Geographic proximity to the donor
- Other factors affecting wait time include body size and sensitization

History of the allocation system

- First system created in 1988
  - Status 1: Highest priority, those requiring mechanical or inotrope support
  - Status 2: Second highest priority
  - Status 7: Those temporarily unsuitable for transplant
- Candidates within each status sorted according to waiting time
- Included geographic zones in 500 mile radius increments

Major changes in 1998

- LVADs becoming more common and more durable
- Status 1 divided into 1A and 1B in effort to prioritize sicker patients on temporary support
- 2005: Further incremental changes in geographic allocation

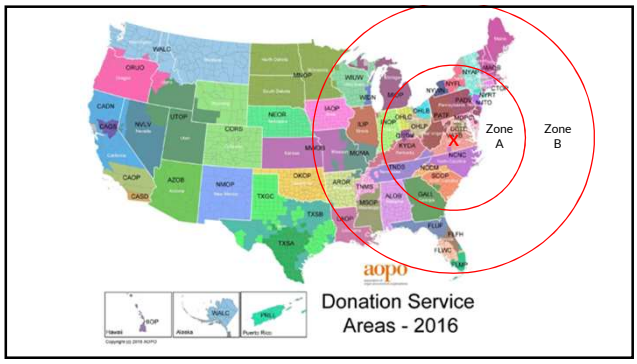
The Previous Allocation System

Previous allocation system

- Status 1A
  - Temporary mechanical circulatory support (ECMO, balloon pump)
  - Mechanical ventilation
  - High dose single inotrope or multiple inotropes with invasive hemodynamic monitoring
  - LVAD complications (pump thrombosis, pump-related infection, GI bleeding, right heart failure, severe AI, ventricular arrhythmias)
- Stable LVAD patient also allotted 30 days of elective time at status 1A

Previous allocation system

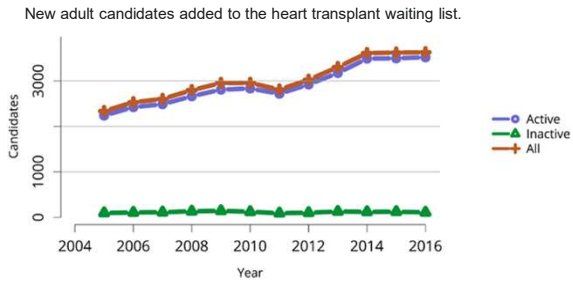
- Status 1B
  - Stable LVAD without complications
  - Low dose inotrope support without hemodynamic monitoring
- Status 2
  - All others not meeting criteria for status 1
- Status 7
  - Those temporarily not suitable for transplant
- Transplant centers can also apply for individual exceptions



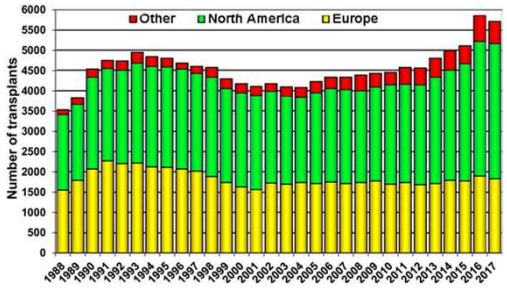
Adult heart allocation 1999–2005		Adult heart allocation 2005 to present	
Local	Status 1A Status 1B Status 2	Local	Status 1A Status 1B
Zone A	Status 1A Status 1B	Zone A	Status 1A Status 1B
Zone B	Status 1A Status 1B	Local	Status 2
Zone A	Status 2	Zone B	Status 1A Status 1B
Zone B	Status 2	Zone A	Status 2
Zone C	Status 1A Status 1B Status 2	Zone B	Status 2
Zone D	Status 1A Status 1B Status 2	Zone C	Status 1A Status 1B Status 2
		Zone D	Status 1A Status 1B Status 2
		Zone E[1]	Status 1A Status 1B Status 2

DM Meyer, et al. American Journal of Transplantation 2015; 15: 44–54

Why Change?



M Colvin, et al. Am J Transplant. 2018;18(Suppl 1):291–362.



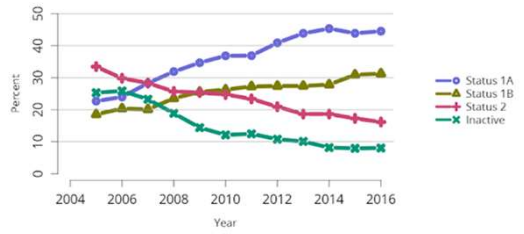
K K Khush, et al. The Journal of Heart and Lung Transplantation, Vol 38, No 10, October 2019

J Hoosain, S Hankins. Curr Cardiol Rep (2019) 21: 67

Concerns with the old system

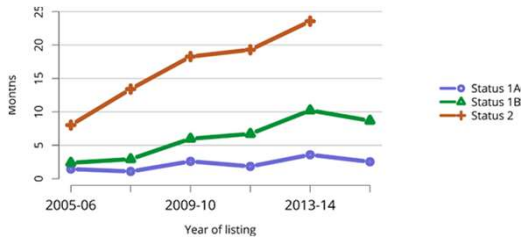
- Too many candidates waiting at status 1A
- Significant heterogeneity in the candidates waiting at 1A
- 1A candidates had 3 fold higher waiting list mortality
- Increased use of temporary and durable mechanical support

Heart transplant candidates status distribution 2004-2016



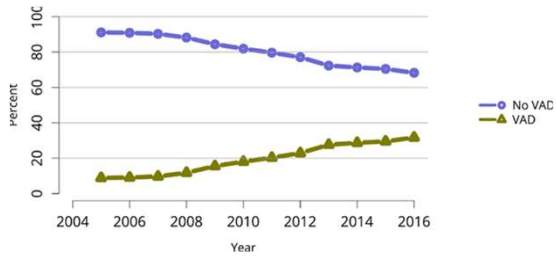
M Colvin, et al. Am J Transplant. 2018;18(Suppl 1):291–362.

Median months to heart transplant for waitlisted adults by medical urgency at listing.



M Colvin, et al. Am J Transplant. 2018;18(Suppl 1):291–362.

Distribution of adults waiting for heart transplant by VAD status at listing



M Colvin, et al. Am J Transplant. 2018;18(Suppl 1):291–362.

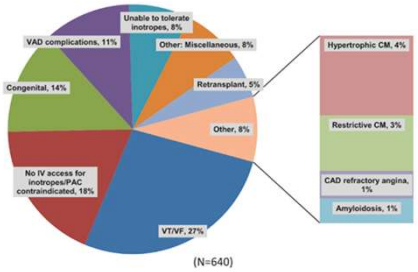
"The proportion of Status 1A candidates has doubled in the past 10 years and now >40% of candidates wait at this highest priority designation, decreasing the likelihood that lower priority candidates are allocated a donor heart (2). Because status is based on therapy and not objective markers of illness, it has been suggested that this trend could be explained in part by transplantation centers "gaming the waitlist" by overtreating less urgent candidates with medically unnecessary therapy to elevate their statuses to the level needed to receive a transplant."

Parker et al. JACC VOL. 71, NO. 16, 2018

Concerns with the old system

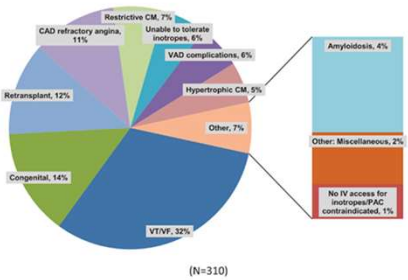
- Too many patients not well accounted for
  - Restrictive or hypertrophic cardiomyopathy
  - Congenital heart disease
  - Ventricular arrhythmias
- Too many exceptions requested

Status 1A exception requests by category



American Journal of Transplantation 2015; 15: 44–54

Status 1B exception requests by category

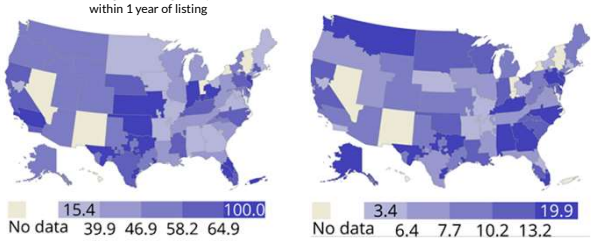


American Journal of Transplantation 2015; 15: 44–54

Concerns with the old system

Percentage receiving transplant within 1 year of listing

Pretransplant mortality rates



M Colvin, et al. Am J Transplant. 2018;18(Suppl 1):291–362.

Revising the allocation system

- Intended to address the following concerns
  - Increase in transplant candidates without an increase in available donors
  - Higher than desirable waiting list mortality for the most urgent patients
  - The increased use of ventricular assist devices

Goals with the new system

- Better risk stratification to prioritize those with the highest risk of dying and improve wait list mortality
- Improve recognition of mechanical circulatory support use
- Ensure appropriate listing with more specific qualifications for status levels
- Provide disadvantaged groups better recognition
- Ensure broader geographic organ distribution

The New Allocation System

New listing criteria

- Previous listing criteria
  - Status 1A
  - Status 1B
  - Status 2
  - Status 7
- New listing criteria
  - Status 1
  - Status 2
  - Status 3
  - Status 4
  - * Status 5
  - Status 6
  - Status 7

Stat

- V

Cardiogenic Shock

1. Systolic BP < 90
2. Cardiac index < 1.8 or < 2.0 if supported by inotropes
3. Pulmonary capillary wedge pressure > 15

Or, if unable to obtain hemodynamics

1. CPR performed
2. Systolic BP < 70
3. Lactate > 4
4. AST or ALT > 1000

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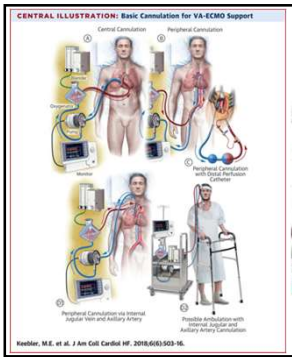
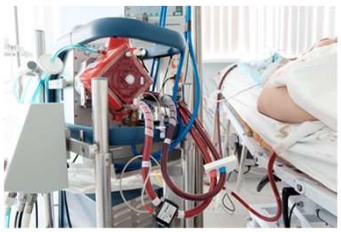
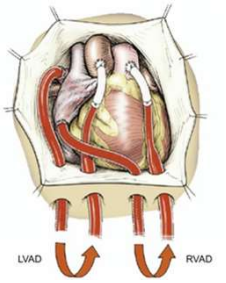




Status 1

- Veno-arterial ECMO
  - Cardiogenic shock or cardiac arrest
  - Must reapply every 7 days to extend status
    - Cannot transition to more durable mechanical support (LVAD)
    - Cannot be weaned off ECMO
- Non-dischargeable, surgically implanted, pulsatile support devices
  - Must reapply every 14 days



Graham Foster, in Mechanical Circulatory and Respiratory Support, 2018

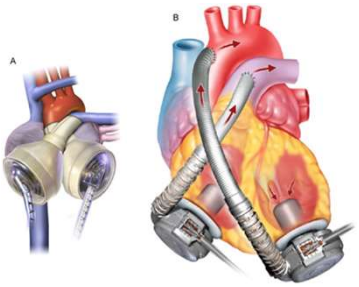
V Horvath, et al. Cor et Vasa. Vol 55; 4:320-323

Status 1

- Mechanical circulatory support with life-threatening arrhythmias
  - Needing biventricular MCS due to ventricular arrhythmias, or
  - Multiple separate episodes of VT/VF, and
    - Not a candidate for other therapies such as ablation
    - Normal electrolytes
    - Required electrical cardioversion despite continuous IV antiarrhythmic medication
  - Must reapply every 14 days

Status 2

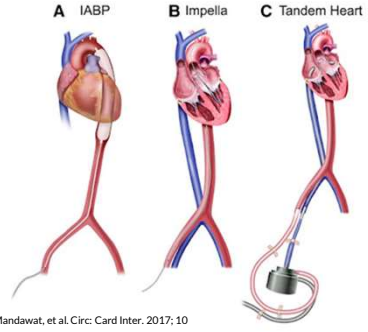
- Total artificial heart
- RVAD
- BiVAD



(A) SynCardia total artificial heart and (B) biventricular support using two HeartWare® HVADs, EC McGee, et al. Ann Thorac Surg. 91 (2011) e1-e3.

Status 2

- Total artificial heart
- RVAD
- BiVAD
- Non-dischargeable, surgically-implanted LVAD with shock
- Percutaneous endovascular MCS with shock
- Intra-aortic balloon pump with shock



A Mandawat, et al. Circ: Card Inter. 2017; 10

Status 2

- Total artificial heart
- RVAD
- BiVAD
- Non-dischargeable, surgically-implanted LVAD with shock
- Percutaneous endovascular MCS with shock
- Intra-aortic balloon pump with shock
- MCS with severe malfunction
  - Causing imminent danger and requires entire device replacement
- Recurrent ventricular arrhythmias

Status 3

- Multiple inotropes or single high dose inotrope with invasive hemodynamic monitoring (Swan catheter) with shock
- Mechanical circulatory support (LVAD) with complication
  - Hemolysis
  - Pump thrombosis
  - Right heart failure
  - Device infection
  - Mucosal bleeding
  - Aortic insufficiency

Status 4

- All other LVAD patients
- Inotropes without invasive hemodynamic monitoring
- Congenital heart disease
- Ischemic heart disease with intractable angina
- Amyloidosis, hypertrophic, or restrictive cardiomyopathy
  - With intractable angina, poor hemodynamics, or VT/VF
- Re-transplant patients
  - With recurrent heart failure ot significant allograft vasculopathy

Status 5

- Heart transplant candidates also listed for at least one other organ

Status 6

- All other candidates not fitting other criteria

Status 7

- All candidates who are temporarily not suitable for transplant

Adult heart allocation 2005 to present	
Local	Status 1A Status 1B
Zone A	Status 1A Status 1B
Local	Status 2
Zone B	Status 1A Status 1B
Zone A Zone B	Status 2 Status 2
Zone C	Status 1A Status 1B Status 2
Zone D	Status 1A Status 1B Status 2
Zone E[1]	Status 1A Status 1B Status 2

Changes in geographic allocation

Status 1	500 miles
Status 2	500 miles
Status 3	250 miles
Status 1	1000 miles
Status 2	1000 miles
Status 4	250 miles
Status 3	500 miles
Status 5	250 miles

Status 3	1000 miles
Status 6	250 miles
Status 1 → 3	1500 miles
Status 4 → 6	500 miles
Status 1 → 3	2500 miles
Status 4 → 6	1000 miles
Status 4 → 6	1500 miles
Status 4 → 6	2500 miles

Sample Case

Sample Case

- 56 year old female with a non-ischemic cardiomyopathy, LV EF 15%
- Multiple heart failure hospitalizations
- Advanced NYHA class 3 symptoms
- Struggling with fluid overload despite Bumex 3mg BID
- Only tolerating low dose medical therapy due to symptomatic low BP
- Undergoes evaluation and initially listed at status 6

Sample Case

- Admitted several months later with heart failure exacerbation
- BP 98/62, HR 92
- Right heart cath: cardiac index of 1.9 and a wedge pressure of 18
- Started on milrinone at 0.25 mcg/kg/min
- Symptoms improve with milrinone and diuresis
- Discharged with home milrinone therapy
- Upgraded to status 4

Sample Case

- Returns 2 months later with increased fatigue, dyspnea, poor appetite
- BP 87/58, HR 110
- Right heart cath: cardiac index 1.6 and wedge pressure of 25
- Swan catheter left in place and started on dobutamine 5 mcg/kg/min
- Remains in ICU and upgraded to status 3

Sample Case

- Hemodynamics initially improve with dual inotrope support
- However, 5 days later hemodynamics worsen again
- BP 86/60, cardiac index 1.8, nd wedge pressure of 20
- Intra-aortic balloon pump placed
- Upgraded to status 2
- Transplanted 3 days later!

Evaluating the New Allocation System

Questions to address

- Has the mortality rate for those on the waiting list decreased?
- How have post-transplant survival rates changed?
- Has the geographic distribution of donor hearts changes?

Concerns with the new system

- Will it influence providers to overuse potentially risky therapies?
- Will prioritizing patients on mechanical support lead to worse outcomes?

The Journal of
Heart and Lung Transplantation

RAPID COMMUNICATION

An early investigation of outcomes with the new 2018 donor heart allocation system in the United States

Rebecca Cogswell, MD,[a] Ranjit John, MD,[b] Jerry D. Estep, MD,[c] Sue Duval, PhD,[a] Ryan J. Tedford, MD,[d] Francis D. Pagani, MD,[e] Cindy M. Martin, MD,[a] and Mandeep R. Mehra, MD, MSc[f]

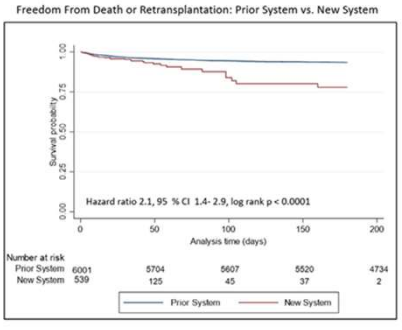
The Journal of Heart and Lung Transplantation, Vol 39, No 1, January 2020

Outcomes with the new heart allocation system

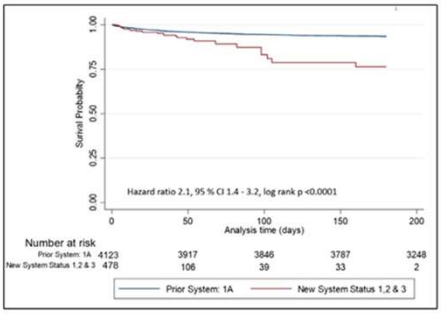
- Included 539 transplant done within the first 5 months of the new system
- 83% of transplant were done from status 1, 2, and 3
- Overall results suggest some improvement in mortality on the wait list but worsened post-transplant outcomes

Outcomes with the new heart allocation system

- 180-day survival was 77.9% in the new system vs 93.4% in the old system
- Hemodynamics on right heart cath were worse in the new system
- Less likely to have an LVAD at the time of transplant: 23% vs 42%
- More likely to have temporary mechanical support: 41% vs 10%
- More likely to be on ECMO: 6.5% vs 1.6%
- 180-day survival on the wait list was 95% in the old system vs 96.1% in the new



Freedom from Death or Re-transplantation: Prior System 1A vs. New System Status 1,2,3



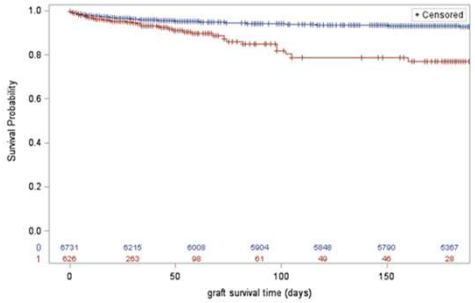
ASAIO JOURNAL

"Unintended" Consequences of Changes in Heart Transplant Allocation Policy: Impact on Practice Patterns

Jaimin R. Trivedi and Mark S. Slaughter

Trivedi, Jaimin R.; Slaughter, Mark S. ASAIO Journal. 66(2):125-127, February 2020.

Patient Characteristics	Listed Before October 2018	Listed After October 2018	*p*
ECMO at listing	1.8%	2.7%	0.02
IABP at listing	5.3%	10.3%	<0.01
ECMO at Tx	1.2%	7.6%	<0.01
IABP at Tx	9.4%	32.8%	<0.01
LVAD at listing	31%	29%	0.07
LVAD at Tx	41%	24%	<0.01
Biventricular support @ listing	1.3%	2.1%	0.02
Biventricular support at Tx	2.5%	4.8%	<0.01
Ischemia time (hr)*	3.0 (2.3–3.7)	3.4 (2.8–4.0)	<0.01
Distance (miles)*	82 (13–261)	243 (72–443)	<0.01
Wait time (days) for Txed patients*	73 (24–189)	14 (6–35)	<0.01
Transplantability† at (months)			
1	19%	31%	<0.01
3	36%	42%	<0.01
6	48%	45%	0.02
Post-Tx mortality (months)			
1	4%	5%	0.3
3	6%	15%	<0.01
6	7%	23%	<0.01



"We believe that there is a reasonable chance that a larger and longer experience will reverse these early troubling trends."

Thank You

LVAD Evaluation and The New Devices

Presented by Theresa Guyton, MSN, RN, AG-ACNP, CHFN
And Kelly Wozneak, MSN, RN, ACNP, CHFN
With additional content from Carole Ballew, ACNP, CCTC, CHFN

Disclosures

There are no affiliations that interfere with this presentation content.

Objectives

- To discuss the definitions and epidemiology of advanced heart failure
- To discuss the latest technology advances for LVAD
- To discuss the LVAD evaluation process and supporting evidence-based guidelines.

Just so we are on the same page…

Heart Failure:

Clinical syndrome results from **structural or functional impairment**

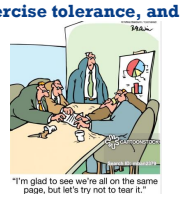
Caused by disorders of pericardium, myocardium, endocardium, heart valves, or great vessels

Cardinal manifestations: dyspnea, fatigue that can limit exercise tolerance, and fluid retention.

50/50 HFrEF/HFpEF

Estimated 9 million people in US by 2030

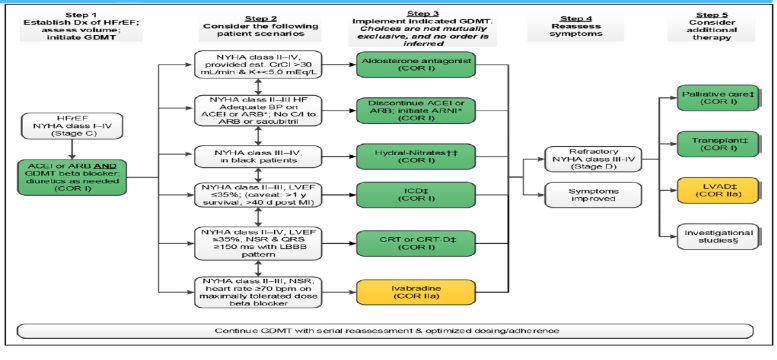
50% die w/in 5 years of 1st admit



"I'm glad to see we're all on the same page, but let's try not to tear it."

ACCF/AHA Stages of HF: Structural Classification		NYHA Classes of HF: Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	**Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.**
D	**Refractory HF requiring specialized interventions.**	IV	**Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.**

We aim for success with GDMT



But unfortunately, things can go downhill

NYHA Class III:

- Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes heart failure symptoms

NYHA Class IV:

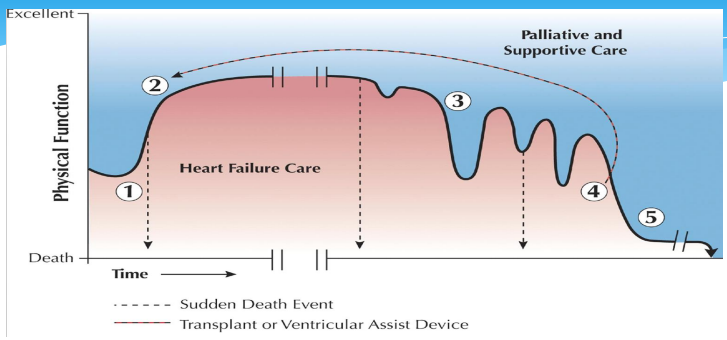
- unable to carry on any physical activity without symptoms of heart failure, or symptoms of heart failure at rest

ACC/AHA Stage D: refractory heart failure requiring specialized interventions

Advanced Heart Failure

- Hospitalizations
- Renal function
- Weight loss
- Intolerance to GDMT (hypotension)
- Persistent DOE and/or dyspnea at rest
- Hyponatremia (< 133)
- Escalation of diuretics, +/- use of metolazone
- ICD frequent shocks

HF Trajectory



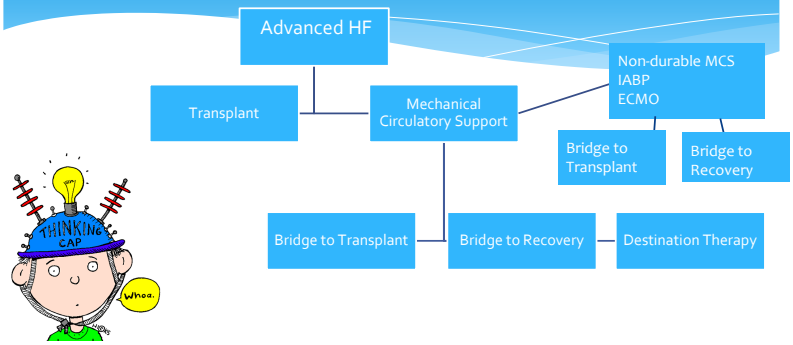
Journal of the American College of Cardiology Jul 2009, 54 (5) 386-396; DOI: 10.1016/j.jacc.2009.02.078

When it gets to this point, oral medications alone are not enough

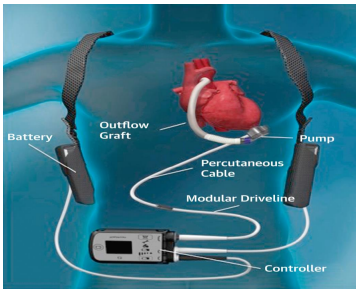
Table 27. Recommendations for Inotropic Support, MCS, and Cardiac Transplantation

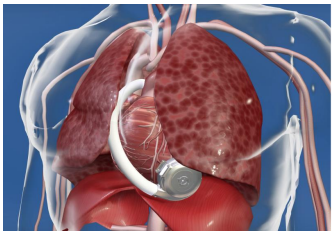
Recommendations	COR	LOE	References
Inotropic support			
Cardiogenic shock pending definitive therapy or resolution	I	C	N/A
BTT or MCS in stage D refractory to GDMT	IIa	B	647,648
Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HF/EF	IIb	B	592,649,650
Long-term support with continuous infusion palliative therapy in select stage D HF	IIb	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
MCS			
MCS is beneficial in carefully selected* patients with stage D HF in whom definitive management (e.g., 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/EF	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

Treatment Algorithm for Advanced Heart Failure

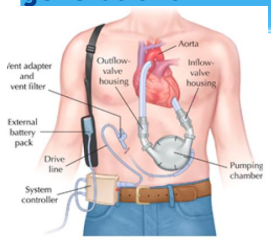


What's so special about LVADs?





How did we get to this point? 1st, 2nd, and 3rd generations



HeartMate XVE LVAS

HeartMate II

HeartMate III

What have we learned along the way?

First Generation:

- Pneumatic pump, pulsatile flow, pre-peritoneal pocket
- Survival 6-12 months
- Very large in the body
- Required large energy supply
- Batteries lasted 30 minutes (pneumatic) to 3-4 hours(Heartmate VE, XVE)
- Complications: stroke, infection, device malfunction

What have we learned along the way?

Second Generation:

- Axial flow, continuous flow, pre-peritoneal pocket
- Smaller with better survival
- Required a smaller energy supply, batteries lasted longer
- Bearings without as much wear
- Risks of stroke, infection, device malfunction, and GI bleeding

3rd Generation: Centrifugal, Continuous flow, Pericardial space

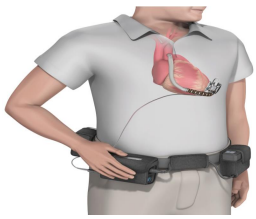
Heartmate 3

- Fully magnetically levitated
- Large, consistent blood flow pathways= less shear stress
- Intrinsic pulsatility= reduce stasis and minimize thrombus

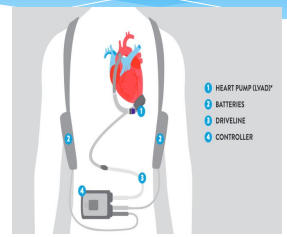
Heartware HVAD

- Passive maglev with hydrodynamic bearings= no mechanical bearings, less friction and heat
- Dual motor stators= enhanced efficiancy

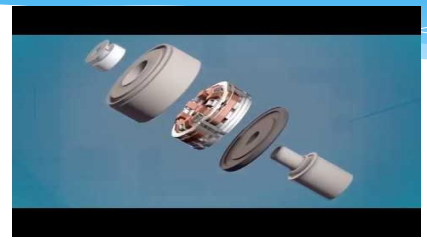
Heartware HVAD



Heartmate 3



Heartmate 3



https://youtu.be/IbHN8e_OGJw

What's New About LVADs

HeartMate 3- MOMENTUM Trial

- **Compared HeartMate 2 vs HeartMate 3 (not the HeartWare VAD)**

AXIAL FLOW

CENTRIFUGAL FLOW

HeartMate 3- MOMENTUM Trial

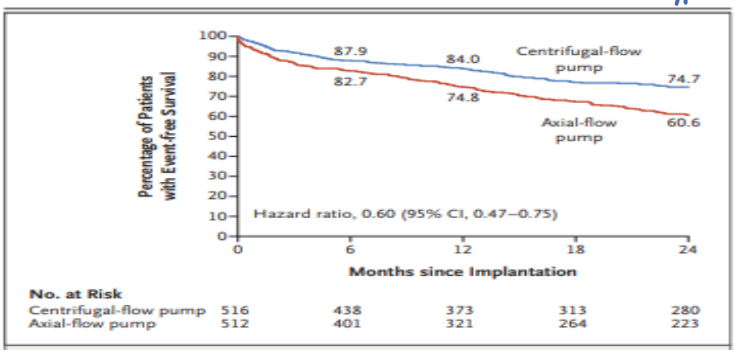
- Outcomes studied:
  - Survival
  - Complications
    - Stroke
    - GI bleeding
    - Pump Thrombosis

MOMENTUM Trial Results

Table 2. Primary and Principal Secondary End Points.*

End Point	Centrifugal-Flow Pump Group (N=516)		Axial-Flow Pump Group (N=512)		Absolute Difference	Relative Risk (95% CI)	P Value
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*	*percentage points (95% LCB)*		
Primary end point†							
Noninferiority analysis	397	76.9 (73.1–80.5)	332	64.8 (60.5–69.0)	12.1 (6.0)		<0.001‡
Superiority analysis	397	76.9 (73.1–80.5)	332	64.8 (60.5–69.0)		0.84 (0.78–0.91)	<0.001‡
First event that resulted in treatment failure with respect to the primary end point§							
Withdrew before implantation	1	0.2 (0.0–1.1)	7	1.4 (0.6–2.8)		0.14 (0.02–1.15)	
Withdrew after implantation	4	0.8 (0.2–2.0)	3	0.6 (0.1–1.7)		1.32 (0.30–5.88)	
Underwent reoperation to replace or remove pump¶	14	2.7 (1.5–4.5)	73	14.3 (11.4–17.6)		0.19 (0.11–0.33)	
Had disabling stroke‖	20	3.9 (2.4–5.9)	30	5.9 (4.0–8.3)		0.66 (0.38–1.15)	
Died within 24 months after implant**	80	15.5 (12.5–18.9)	67	13.1 (10.3–16.3)		1.18 (0.88–1.60)	
Principal secondary end point††							
Pump replacement within 24 months after implantation	12	2.3 (1.2–4.0)	57	11.3 (8.7–14.4)		0.21 (0.11–0.38)	<0.001‡‡

MOMENTUM Trial- Event Free Survival



Adverse Event	Centrifugal-Flow Pump	Axial-Flow Pump	Centrifugal-Flow Pump	Axial-Flow Pump	Relative Risk (95% CI)	P Value
	no. of patients with events (%)		*events per patient-yr*			
Suspected or confirmed pump thrombosis	7 (1.4)	70 (13.9)	0.01	0.12	0.08 (0.04–0.16)	<0.001
Any stroke	51 (9.9)	98 (19.4)	0.08	0.18	0.42 (0.30–0.57)	<0.001
Disabling stroke	26 (5.0)	38 (7.5)	0.04	0.07	0.54 (0.34–0.85)	0.008
Any bleeding	225 (43.7)	278 (55.0)	0.61	0.95	0.64 (0.57–0.72)	<0.001
Gastrointestinal bleeding	126 (24.5)	156 (30.9)	0.31	0.49	0.64 (0.54–0.75)	<0.001
Other neurologic event	59 (11.5)	47 (9.3)	0.09	0.08	1.25 (0.88–1.79)	0.21
Any major infection	300 (58.3)	285 (56.4)	0.82	0.82	1.00 (0.89–1.12)	0.96
Right heart failure	176 (34.2)	143 (28.3)	0.27	0.23	1.15 (0.94–1.42)	0.18
Cardiac arrhythmia	185 (35.9)	207 (41.0)	0.37	0.45	0.82 (0.70–0.97)	0.02
Respiratory failure	111 (21.6)	98 (19.4)	0.19	0.17	1.10 (0.86–1.40)	0.44
Renal dysfunction	73 (14.2)	56 (11.1)	0.11	0.08	1.36 (0.98–1.89)	0.07
Hepatic dysfunction	25 (4.9)	27 (5.3)	0.03	0.04	0.78 (0.46–1.34)	0.38

WHAT IS IN THE FUTURE?

Transcutaneous Energy Transfer System

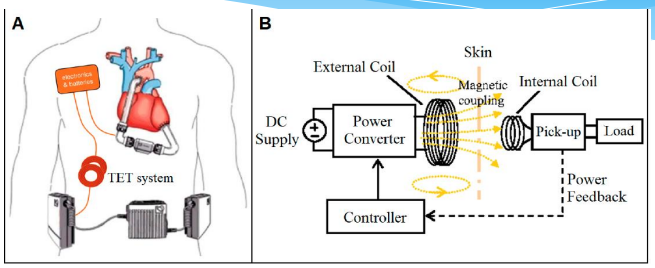


Figure 6. Schematics of the TET system (**A**) in patient use and (**B**) with an electromagnetic coupling between the internal and external coils located inside and outside of patient skin, respectively [100,101].

Muscle Powered VADs

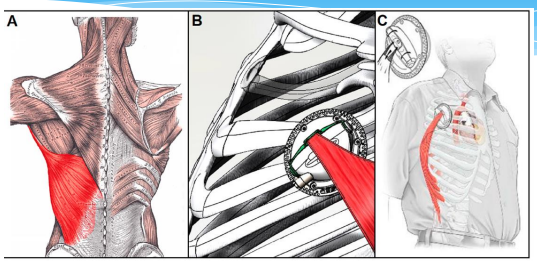


Figure 7. Muscle-powered VADs could use the latissimus dorsi (**A**) as its power source and convert this endogenous muscular power into hydraulic energy via a completely implantable muscle energy converter (**B**) that can potentially power pulsatile VADs for long-term use (**C**) [103,106,107].

Non blood Contacting

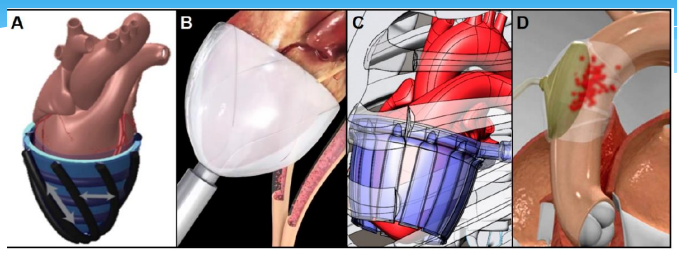


Figure 8. Biomimetic (**A**), minimally invasive (**B**), and muscle-powered (**C**) soft robotic direct cardiac compressive sleeves (DCCS) use copulsation and extra-aortic balloon pumps (EABP) (**D**) use counterpulsation techniques to enhance cardiac function without directly interacting with the bloodstream [107,108,113,114,117].

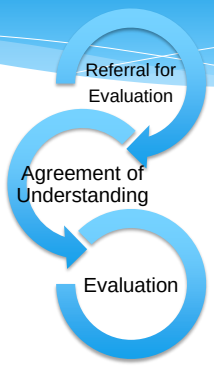
To Sum it up:

Category	Product	Type of Support	Duration of Support	Advantages	Limitations
3rd Generation—Continuous Centrifugal Flow	HeartWare HVAD	LVAD	Long-term	Small size, magnetically levitated rotor, FDA approval for DT in 2017	Risks of infection, bleeding, arrhythmia, stroke
	HeartMate III	LVAD	Long-term	Magnetically levitated rotor, FDA approval for DT in 2018	Risks of infection, bleeding, arrhythmia, stroke
	DuraHeart	LVAD	Long-term	Favorable clinical outcomes as BTT in Japan and Europe	Hemolysis, thromboembolism, bleeding
	HeartWare MVAD	LVAD	Long-term	Miniature size for pediatric uses	Risks of infection, bleeding, and thrombosis
	CentriMag	Uni-VAD	Short-term	Magnetically suspended rotor for acute therapy, Minimal shear force on RBCs and hemolysis	Bleeding, infection, respiratory failure, hemolysis, neurologic dysfunction
Non-blood-contacting VADs	CorInnova	Ventricular Epicardium	Potentially Long-term	Minimally invasive, Non-blood-contacting, soft material	Studies done on large animals only
	Biomimetic DCCS	Ventricular Epicardium	Potentially Long-term	Soft material, Non-blood-contacting, compression and torsion applications	Still under development
	Muscled-powered DCCS	Ventricular Epicardium	Potentially Long-term	Tether-free, Non-blood-contacting, Biocompatible soft material	Still under development
	C-pulse Device	Ascending Aorta	Short-term	Non-blood-contacting	No longer commercially available

So what makes a patient a candidate for a VAD??

Let's start at the very beginning ♪ ♪ ♪

https://www.youtube.com/watch?time_continue=3&v=7s3S-Kg6AA8



How do we deem patients VAD/TP appropriate? Teamwork is the name of the game! Medicare requires the following:

"Beneficiaries receiving VADs for [BTT, BTD or] DT **must be managed by an explicitly identified cohesive, multidisciplinary team of medical professionals with the appropriate qualifications, training, and experience.** The team embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. **Collectively, the team must ensure that patients and caregivers have the knowledge and support necessary to participate in shared decision making and to provide appropriate informed consent."**

And of course, the facility must be CMS certified for VAD implantation.

https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=268

The patient is deemed appropriate for Evaluation: Time to have the talk

VAD Agreement of Understanding (AOU)- the initial informed consent

* Procedure, risks and benefits as well as expectation of the patient and caregiver are explained thoroughly by a VAD coordinator prior to signing
* Signed by **patient and caregiver**
* Separate AOU's are signed for VAD & Transplant. (There are separate consent forms for the actual surgeries).
* We explain to the patient and family that signing this agreement **does not guarantee they will receive VAD or TP**

VAD Agreement of Understanding

Here are the things we review during the initial AOU discussion:

* Explaining the options: BTT, BTR, BTD, DT, or none
* How does the VAD work?
* Survival rates
* Complications associated with VADs
* Responsibilities
* Body image considerations
* Functional capacity and quality of life

The Referral is the first step: LVAD Inclusion Criteria

- Severe heart failure (NYHA III and IV) on full medical management
- At significant risk for cardiac death within one year
- No alternative treatment options
- History of medical compliance/good support system
- Age preferably less than 65, but not limited- No age limit for LVAD –however, must have the expectation of living a year after implant

Absolute Exclusion Criteria

- Medical condition that is expected to limit 1 year survival.
- Active infection not being treated
  (can reconsider once infection treated)
- Other potential roadblocks:

Indications For LVAD, continued…

Life Expectancy Less Than 50% at 6 Months

Accepted -

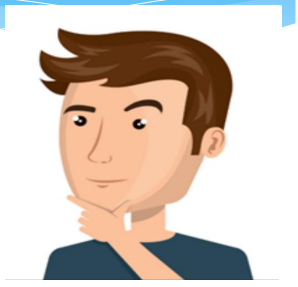
1. Maximum VO2 <10ml/kg/min
2. Severe ischemia not amenable to Rx
3. VT/VF refractory to therapy

Probable -

1. Maximum VO2 <14ml/kg/min
2. Recurrent USAP not amenable to Rx
3. Recurrent CHF refractory to Rx

Peak oxygen consumption & expected benefit after transplantation

Peak oxygen consumption (VO2)	Estimated 1 year survival with Heart Failure (%)	Estimated 1 year survival after transplant (%)
<10	<50	<80-90
10-14	60-75	80-90
14-18	75-85	80-90
>18	85-95	80-90



Risk Stratification

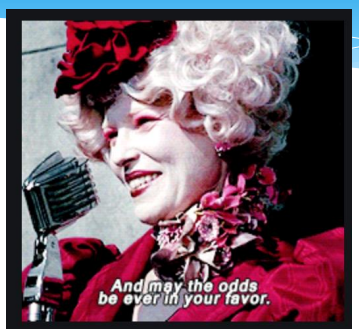
Currently requiring ECMO, MCS, or intropes?

Is ventricular function unrecoverable?

Is this patient too ill to maintain normal hemodynamics and vital organ function with temporary MCS?

Is there capacity for meaningful recovery of end-organ function and quality of life?

Let the Evaluation Begin!



The MCS/TP Candidacy Evaluation: Begins with signing the AOU(s), then a Financial evaluation, then we proceed with:

Age-appropriate cancer screenings

Labs

Serologies & Pre-formed antibody testing for transplant

Imaging

Social Work Evaluation

Dietician Evaluation

Surgical consult

Palliative Care Consult for VAD workups

Dental Consult

Pharmacy Evaluation

Occupational Therapy Evaluation

Physical Therapy Evaluation

And finally, Meeting of the Transplant Interdisciplinary Team to decide candidacy

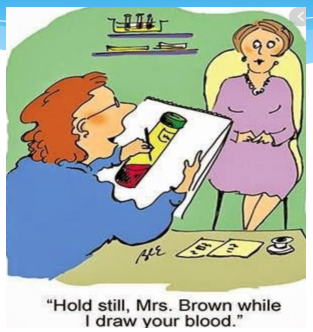
Age Appropriate Cancer Screenings and Lab Work

Cancer Screenings

Comprehensive metabolic panel

CBC and Coags

*Keep in mind, throughout the Evaluation, we are looking for REVERSIBLE conditions!

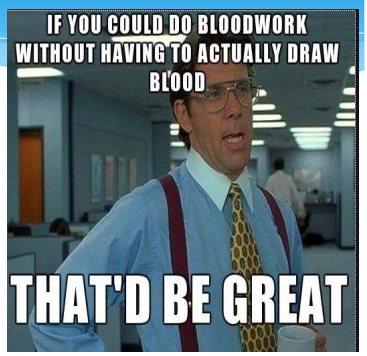


And more labs…..

24 hour urine Creatinine Clearance and Total Protein

Hemoglobin A1C

Serologies

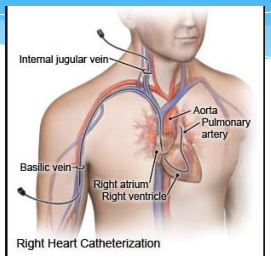


More poking and prodding…

Left Heart catheterization

Right Heart Catheterization

Echocardiogram



Management of infection risk:

Dentistry consult

All unnecessary lines and catheters are removed prior to MCSD implant.

Vaccinations reviewed/updated

The inquisition continues…

Carotid dopplers

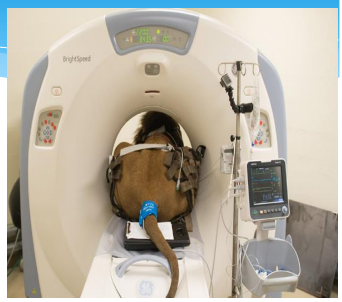
ABI/LE dopplers

Pulmonary Function Testing

Cardiopulmonary exercise test (VO_2) if possible

CT Chest/Abdomen/Pelvis

Liver Ultrasound in setting of elevated LFTs



Social Work Evaluation

Performs SIPAT screening tool, which includes:

- Substance abuse assessment
- Tobacco use
- Caregiver burden
- Psychological/psychiatric evaluation
- Assessment of adherence to medical therapy and social network
- In addition, our Social Worker created an LVAD social support document for the patients & caregivers to review and sign to confirm they understand what the patient will need and what is expected of the caregivers.

Dietician Evaluation

Nutritional assessment

Body mass index

Recommendations/nutritional planning and goals

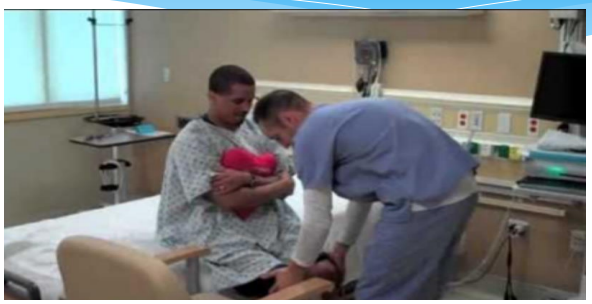
Occupational Therapy Evaluation

MoCA- Can they do what they need to do?

Physical Therapy Evaluation

Begins with regular PT evaluation as pertains to any new eval
Then our PTs will explain eval process specific to VAD eval &:

Function
6 min walk
Home
Frailty



Pharmacy Evaluation

PharmDs performs an in person (if possible) interview and chart review preop:

Allergies

Current meds

Review w/pt and family need for anticoagulation as long as they have the device

Palliative Care Consult

Assist with advanced care planning

Assessment of Symptoms

Review medical history and current medications

Give recommendations for pain and symptom management

Help with assessing pt ability to cope wiht VAD and/or transplant

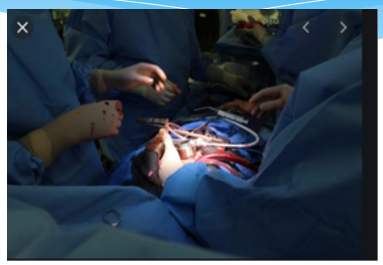
Provide ongoing care as indicated

Surgical Consult

TCV Surgery Evaluation:

The surgery team determines the patient's overall surgical risk

And appropriateness for VAD and/or Transplant, and in conjunction with the multidisciplinary team decide whether (and which surgery/device) should be performed.



Then we put it all together at the Meeting of the Interdisciplinary Team

We meet ever Tuesday morning:

TCV Surgeons, Heart Failure Attendings, VAD and Transplant Coorinators, PT & OT, Pharmacist, Financial Counselor, Social Worker, and Dietician all are present.

And the appropriateness of the decision to offer a patient surgery is made based on each member's input.

This is what we all work for, the chance to give someone time they would not have had otherwise.

Time to wait for a transplant, and time to live the life!

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http://www.clipartpanda.com/categories/thinking-cap-clipart (Image for thinking cap)

https://www.google.com/search?q=image+of+patient+eating+hospital+food+cartoon&sxsrf=ACYBGNQzsYUdevfnhhNFy9bvfgew8MTydw:1581478615892&tbm=isch&source=iu&ictx=1&fir=DitDV3Wphbu8bM%253A%252CUeFxABmXXLJkxM%252C_&vet=1&usg=AI4_-kThOUkZuGbjbN6W4Jo_zTnEBnzzwA&sa=X&ved=2ahUKEwiO4Pr4isvnAhVyIXIEHZ3UC9QQ9QEwA3oECAkQCg#imgrc=XD-y0-YkilGDmM&imgdii=BGx94tr9qY8L_M (image for pt on scale)

https://www.google.com/search?q=image+of+happy+lvad+patient&sxsrf=ACYBGNSpQpuqgaD3Vw0AI7Tj7SX-TWAprQ:1581481407993&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiTiKuslcvnAhVqlHIEHX1LBNEQ_AUoAXoECA0QAw&biw=1280&bih=529#imgrc=i_tvOAJWpRBChM (image of happy lvad pt)

https://www.google.com/search?q=image+of+Physical+therapist+working+with+cardiac+surgery+patient&sxsrf=ACYBGNQ__qgoE-5GQ3ih3NzIfBH7IQo4-Q:1581481577790&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiU06b9lcvnAhVJI3IEHYRbBtYQ_AUoAXoECA0QAw&biw=1280&bih=529#imgrc=K7v-ef_rSmhhQM(image of PT working w/cardiac surgery pt)

https://www.google.com/search?q=image+of+pharmacist+reviewing+med&sxsrf=ACYBGNSMusM_3CFHN14LQ7MJa3SiKtacVA:1581482985827&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiNrtqcm8vnAhXzlHIEHYIwBtUQ_AUoAXoECA0QAw&biw=1280&bih=529#imgrc=csopl_7CaHHM7M (image of pharmacist reviewing meds s.pt)

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https://thoracickey.com/triage-vads-tandemheart-impella-and-centrimag/ image for Tandem Heart

Thank you!!!!!

Questions?

Comments?

APPROACHING PATIENTS WITH PULMONARY HYPERTENSION

Lauren Bedard RN, BSN, CCRN
Heart & Vascular Center: CCU Medicine
Andrew D. Mihalek, MD
Division of Pulmonary & Critical Care Medicine

Disclosure(s)

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  - Complexa, Inc
  - Corvia Medical, Inc
  - United Therapeutics
- Ms. Bedard has no financial disclosures to make
- Practice guidelines for PHTN are ever changing; this session may (i.e. most likely) refer to non-FDA treatment practices
  - **Institutional practice biases abound**

Session objectives

- Review currently accepted diagnostic criteria for pulmonary hypertension & address basics of a pulmonary hypertension evaluation
- Explore various treatment options available managing patients with pulmonary hypertension
- Address & discuss complications associated with therapeutic plans in pulmonary hypertension patients

WHAT EXACTLY IS "PULMONARY HYPERTENSION?"

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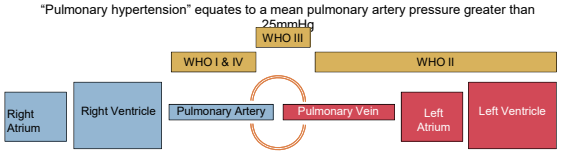
Division of Pulmonary & Critical Care Medicine

"Pulmonary Hypertension" is an umbrella term for a family of diseases

"Pulmonary hypertension" equates to a mean pulmonary artery pressure greater than 25mmHg



"Pulmonary arterial hypertension" refers to pathology "exclusive" to pulmonary artery

Current diagnostic criteria:
- o Mean pulmonary artery pressure (mPAP) greater than 25mmHg
- o Pulmonary arterial occlusion pressure (wedge) less than 15 mmHg
- o Pulmonary vascular resistance (PVR) greater than 3 woods units

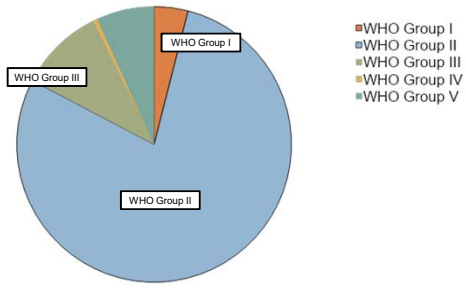
"Pulmonary Hypertension" is an umbrella term for a family of diseases

- Group 1: Pulmonary Arterial Hypertension (PAH)
  - Idiopathic PAH
  - Heritable (BMPR2, ALK1)
  - Connective Tissue Diseases
  - HIV Infection
  - Persistent PH of the Newborn
  - Congenital Heart Defects
  - Portal Hypertension
  - Drug Effect
  - Idiopathic
  - Schistosomiasis
- Group 2: PH Owing to Left Heart Disease (Pulmonary Venous Hypertension)
  - Systolic HF, Diastolic HF, or Valvular Disease
- Group 3: PH Owing to Chronic Hypoxemia
  - COPD, ILD, OSA, OHS
  - Living at high Altitude
- Group 4: Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
- Group 5: PH with Unclear Mechanisms

Cliff Notes Version

- Group 1 → Disease of Pulmonary Arteries
- Group 2 → Due to HF
- Group 3 → Due to Lung Disease
- Group 4 → Due to Chronic Blood Clots to PAs
- Group 5 → Everything Else/ Unclear Mechanism

Estimates of U.S. pulmonary hypertension prevalence by WHO groupings



Gabbay E et al. AJRCCM 2007
Peacock AJ et al. Eur Respir J 2007
Humbert M et al. AJRCCM 2006

Demographics of PAH

Average age at diagnosis:

Average length of time from onset sx to diagnosis:

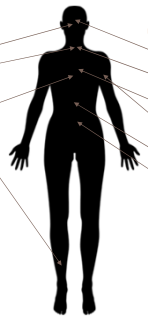
Men vs. Women ?

Mean survival rate @ 1, 3, 5 yrs?

M. Hoeper, JS Gibbs. European Respiratory Review 2014
B. Dunlap, G Weyer Am FAm Physician 2016
R. Benza, D. Miller, et al. Chest Journal 2012

Symptoms of Pulmonary Arterial Hypertension

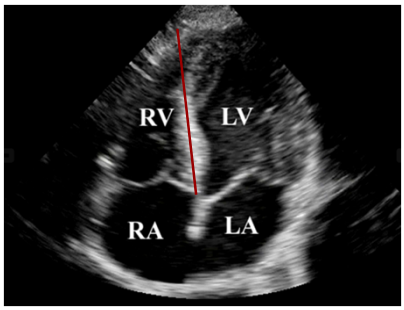
- **Early:**
  - Dizziness
  - Dyspnea
  - Tachycardia
  - LE Edema
  - Fatigue
- **Late:**
  - Syncope
  - SOB
  - Chest Pain
  - Hypotension
  - Hepatomegaly
  - Ascites



McLaughlin VV, Archer SL, Badesch DB, et al. 2009

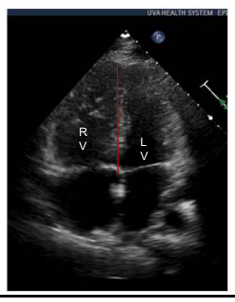
Why do We Care so Much about the Right Ventricle in PH?

Normal Heart
Apical View
4 Chamber

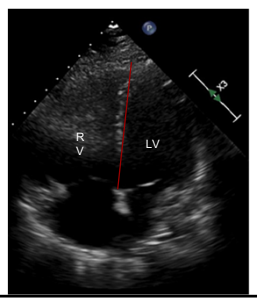


Echocardiographic Changes with PAH Disease Progression

Moderate



Severe



Slide 9

1 This slide can also be turned into a quiz if preferred, for now I have it set for each answer to animate in one by one

Lauren Bedard, 2/12/2020

HOW DO WE KNOW WHEN TO TREAT PULMONARY HYPERTENSION?

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Therapies for WHO I PHTN can be harmful in other types of PHTN

TABLE 3 Discontinuations of PH Therapies

	All Patients (N = 785)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PDE5i ever	696 (88.5)	359 (85.3)	120 (86.3)	1.000	217 (96.0)	<0.001	0.003
Patients with follow-up	618	306	106		206		
PDE5i discontinuations	79 (12.8)	27 (8.8)	14 (13.2)	0.578	38 (18.4)	0.005	0.795
Side effects	23 (3.7)	8 (2.6)	4 (3.8)	1.000	11 (5.3)	0.454	1.000
Efficacy failure	33 (5.3)	9 (2.9)	3 (2.8)	1.000	21 (10.2)	0.003	0.071
Other*	25 (4.0)	11 (3.6)	7 (6.6)	0.801	7 (3.4)	1.000	0.745
ERA ever	322 (41.0)	225 (53.4)	61 (43.9)	0.188	36 (15.9)	<0.001	<0.001
Patients with follow-up	281	190	56		35		
ERA discontinuations	56 (19.9)	28 (14.7)	13 (23.2)	0. 462	15 (42.9)	0.001	0.188
Side effects	36 (12.8)	18 (9.5)	10 (17.9)	0.286	8 (22.9)	0.117	1.000
Efficacy failure	9 (3.2)	4 (2.1)	1 (1.8)	1.000	4 (11.4)	0.066	0.210
Other†	11 (3.9)	6 (3.2)	2 (3.6)	1.000	3 (8.6)	0.447	1.000

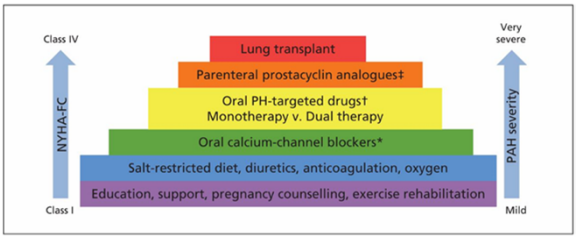
Values are n (%) or n. *Including switch to riociguat. †Including withdrawal of sitaxentan.
Abbreviations as in Tables 1 and 2.

Opitz CF et al. JACC 2016

Management decisions & treatment strategies for PHTN

- WHO (NYHA) Class I:
  - Comfortable at rest
  - Without limitations in physical activity
  - Ordinary activity does not cause symptoms
- WHO (NYHA) Class II:
  - Comfortable at rest
  - Slight limitation in physical activity
  - Ordinary physical activity causes symptoms
- WHO (NYHA) Class III:
  - Comfortable at rest
  - Marked limitation in physical activity
  - Minimal physical activity results in symptoms
- WHO (NYHA) Class IV:
  - Symptoms at rest
  - Inability to conduct any activity without symptoms
  - Display severe symptoms (Overt right sided heart failure, syncope)

Cliff Notes Version



N. Hambly, F Alawfi, S Mehta. CMAJ 2016

HOW DO WE TREAT PULMONARY ARTERIAL HYPERTENSION?

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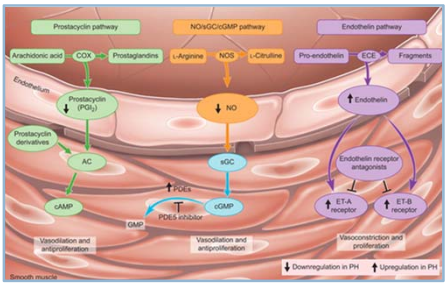
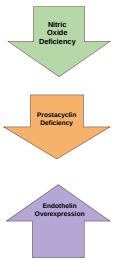
Treatments for PAH seek to reverse consequences of end organ damage



Humbert M. Eur Respir Rev. 2010

Cliff Notes Version for RNs

Imbalance:



3 Vasoactive Pathways involved in PAH:

- Therapy blocks PDE-5 to increase cGMP or stimulates cGMP production
- Therapy compensates for missing prostacyclin
- Therapy blocks endothelin binding to receptors, preventing vasoconstriction and proliferation

Humbert M, Morrel NW, Archer SL, et al. 2004

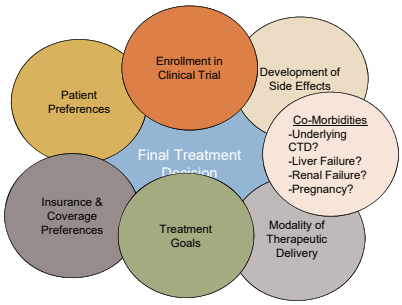
2015 ESC/ERS Guideline Treatment Goals

Risk Assessment Parameters Considered Low Risk in PAH Patients:

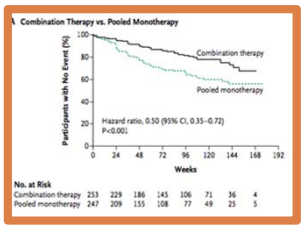
- Absence of RV failure clinical signs
- No progression of symptoms
- No syncope
- 6MWD >440 meters (or improved)
- BNP <50 ng/l
- Imaging showing RA area decreased
  - <18cm^2
- Improved hemodynamics:
  - RAP <8mmHg
  - CI ≥ 2.5 l/min/m^2
  - SvO_2 >65%

Galie N, Hubert M, Vachiery J, et al. 2015

The complexity of treatment decisions in PAH patients



Initiation of dual therapy may be more beneficial than monotherapy



Galie N et al. NEJM 2015

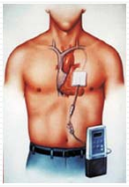
NURSES AS THE GUARDIANS OF PAH PATIENTS ON IV THERAPY

UVA Health

PHA

IV Prostacyclin Therapy

- **Patients with severe PAH on initial presentation to UVA**
- Patients that did not respond to oral therapy and now have disease progression
- Patients who ultimately will require lung transplantation and must attempt and fail all treatment methods (including IV prostacyclin) prior to receiving a transplant.



IV Prostacyclin Therapy Choices

Epoprostenol (Veletri®)

- Half-life **3-5 mins**
- Cassettes or syringes changed at least every **24 hrs**
- More potent dosing

Treprostinil (Remodulin ®)

- Half-life **4 hrs**
- Cassettes or syringes changed at least every **48 hours**
- Higher dose (vs. Veletri®) for similar effect

- Both are potent pulmonary vasodilators
- Both are dosed in ng/kg/min based on a dosing weight that NEVER CHANGES
- Both run continuously via CVL→ protected and solely used for this therapy
  - Standard central line dressing care
- Both are administered via CADD Legacy or Alaris Syringe Pump @UVA Health

Safety Considerations for RNs

- Use dedicated units with specialty trained RNs
- Ongoing competency review Q 1-2 yrs
- Never interrupt, pause, flush, or disconnect this line
- While inpatient or intra-procedure, always have a back-up PIV or CVL port to use
- Know what to do if your pump or line malfunctions
- Keep a backup pump in room and backup cassette/syringe and tubing on unit
- Respond to IV alarms immediately (as a team)
- Use signage to identify these high risk patients
- Competent RN accompanies patient off-unit (guard the line)

KNOW YOUR SYMPTOMS

IV Prostacyclin Side Effects

- Nausea/Vomiting
- GI Distress /Diarrhea
- Jaw Pain
- Leg Pain
- Headache
- Flushing of Skin/Rash
- Minor drop in BP

Toxicity or Withdrawal Symptoms

- Worsening SOB
- Hypoxia/Cyanosis
- Acute/Profound Hypotension
- Syncope
- Chest Pain
- Persistent, Extreme N/V
- “Don’t look good”

SIDE EFFECTS: BE AN ADVOCATE

- Side effects are expected but can be managed
- They should get better over time
- Have PRN orders ready
- Consider scheduling or pre-dosing for symptom relief during uptitration phase
- Think creatively to find the right bundle for your pt
- Patients may just need to sleep through it and that is OK
- Marinol is an option and it works well

Other Considerations

Additional Risks of IV Therapy

- Central line infection: febrile, site assessment, pain at site
- Bleeding Risk (PLT inhibition): coughing or vomiting blood, dark + tarry stools, petechiae

SQ Remodulin is a Thing

- Assess SQ site
- Pts use home CADD MS3 Pump in ER and outpatient
- Inpatient we switch to IV therapy per guideline (1:1 conversion)

WALK IN THEIR SHOES

- Imagine facing a new, debilitating diagnosis and told the IV medicine you are about to start will make you feel horrible at first but ultimately extend your life. Once started, this medicine can never stop. You will manage it all at home and face constant insurance and access hurdles.
- Patients will go through the stages of grief:
  - Shock + Denial
  - Frustration + Anger
  - Guilt + Bargaining
  - Sadness, Fear, Depression
  - ACCEPTANCE

Give them the space to feel and respond to their diagnosis without judgment so they can begin to move forward. Reassure them you are here for them on this journey. **The Pumonary Hypertension Association has resources for you and your patients. Utilize Palliative Care, SW, and Chapliancy!**

CONCLUDING REMARKS

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