# Circulatory Support Devices – Inpatient, Outpatient, and Transitions of Care Considerations for Pharmacists

GMCCP Presentation May 5, 2015

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#### Disclosures



• Within the past 12 months we have no actual or relevant financial relationships.

#### Learning Objectives

- 1. Describe advances in left ventricular assist device (LVAD) technology.
- 2. Discuss indications for LVAD implantation.
- Devise a care plan to assist management of a postoperative LVAD patient.
- 4. Review pharmacotherapy options for the management of complications associated with LVAD patients.
- 5. Apply an understanding of LVAD patient's medication needs to transitions of care opportunities.
- 6. Identify significant challenges LVAD patients encounter as outpatients.

# Mechanical Circulatory Support Devices (MCSDs)

- LVAD, RVAD, BiVAD, TAH
- Components of MCSDs
  - Motor housed within a blood pump
  - Inflow and outflow cannulas
  - Percutaneous driveline
  - Controller
  - Portable power source
  - System monitor

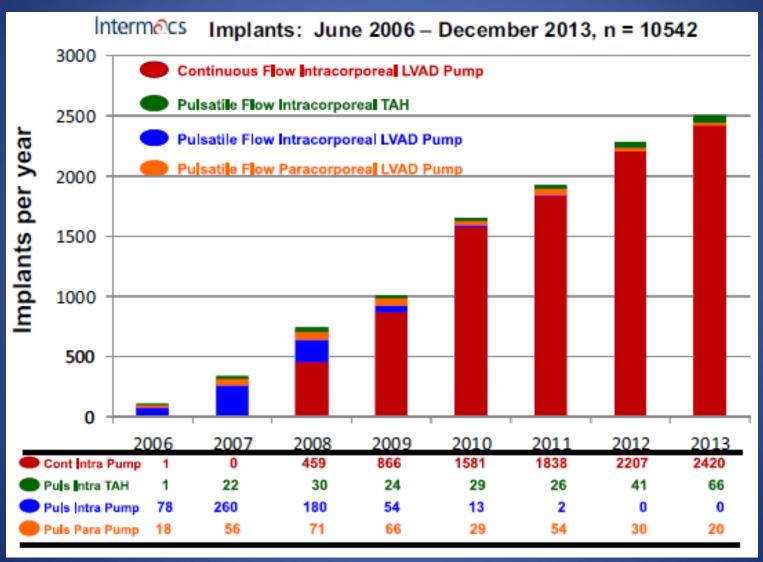
## Chances are you will see an LVAD...

 The number of heart transplants / year has plateaued at ~ 2,200

It is estimated that up to 250,000 patients
 <75 years old have NYHA IIIB / IV HF</li>

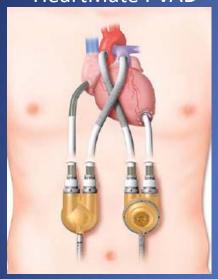
 The number of CF VAD implants in 2013 topped 2,400

#### Adult Implant by Year in the INTERMACS Registry



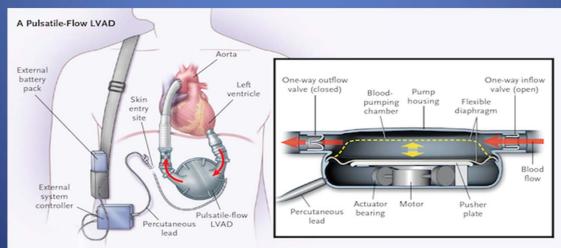
#### **Devices - Past**

#### HeartMate PVAD



#### HeartMate XVE vs. HeartMate II





Reprinted with the permission of Thoratec Corporation. Accessed 4/2015. *N Engl J Med*. 2009;361:2241-2251.

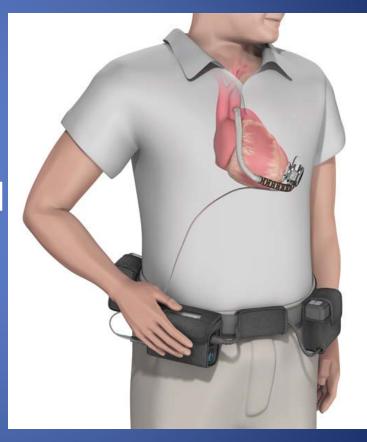
# Thoratec's HeartMate II (HMII)

- FDA approved for:
  - BTT (2008)
  - DT (2010)
- Implanted below the diaphragm
- Speed range: 6,000-15,000 rpm
- Flow range: 3-10 L/min



# HeartWare (HVAD)

- FDA approved for:
  - BTT (2012)
  - DT (ENDURANCE trial)
- Implanted in the pericardial space
- Speed range: 1,800-4,000 rpm
- Flow range: up to 10 L/min



#### **Devices - Future**

#### Thoratec Heartmate III





#### Terumo DuraHeart II





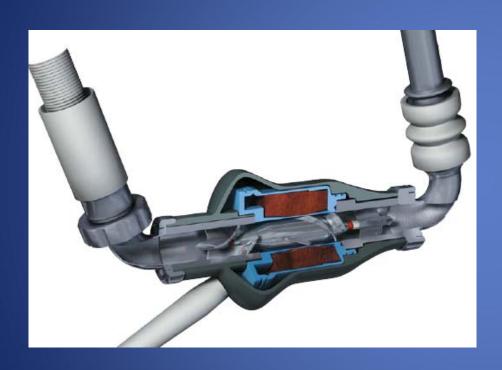
HeartMate X

#### HeartWare MVAD

http://media.corporate-ir.net/media\_files/irol/95/95989/2010AR/shareholders\_letter\_06.html Accessed 4/2015. http://www.heartware.com/media-resources Accessed 4/2015.

http://terumoheart.net/us/index.php/patients-caregivers/duraheart Accessed 4/2015.

# Axial vs. Centrifugal Design





#### **Device Parameters**

- Pump flow (L/min)
- Pump speed (rpm)
  - Only programmable variable
- Pump power (watts)
- Pulse index (pulsatility)
  - Represents the equilibrium between native cardiac function and LV preload with ventricular unloading by the VAD

# Device Physiology

- Pump flow is a function of:
  - Speed

```
↑ speed \rightarrow ↑ flow ↓ speed \rightarrow ↓ flow
```

- Pressure differential
  - Difference in preload (LV chamber pressure) and afterload (mean aortic pressure)

```
\uparrow pressure gradient \rightarrow \downarrow flow \downarrow pressure gradient \rightarrow \uparrow flow
```

- Patients may not have a palpable pulse
- Contraction of the LV will not generate the aortic valve to open with every beat

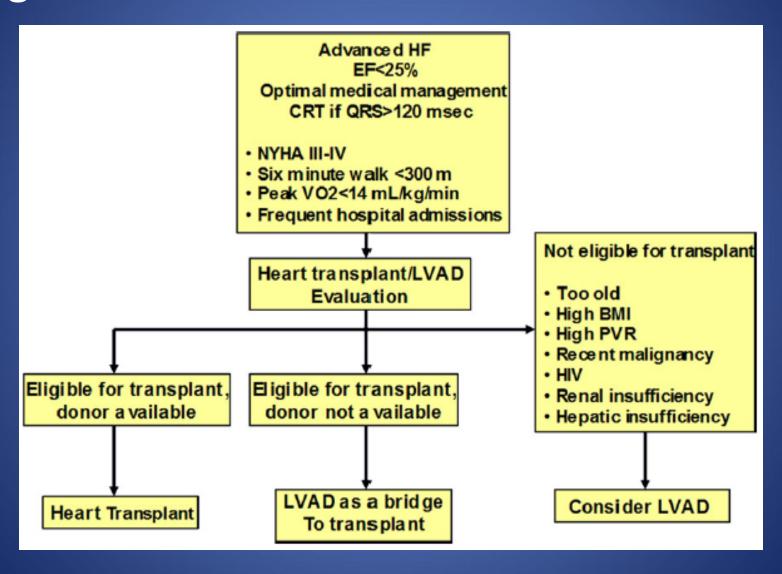
#### **Abnormal Device Conditions**

<b>Device Condition</b>	Potential Causes	Intervention
High flows	Vasodilation Sepsis	Reduce or hold vasodilators Add pressors Look for underlying source of sepsis and treat
Low flows	Hypovolemia Bleeding Arrhythmias	Bolus fluids Address source of bleeding and transfuse Treat arrhythmias
High powers	Pump thrombosis	Add additional antithrombotics Consider thrombolysis Consider device exchange

#### **Abnormal Device Conditions**

<b>Device Condition</b>	Potential Causes	Intervention
High pulsatility	Recovery of LV function  Percutaneous lead damage	Look for evidence of recovery Assess VAD components as appropriate
Low pulsatility	Hypovolemia Very poor native LV function Excessive speed	Bolus fluids Add inotropic support Adjust pump speed
Suction Event	Hypovolemia Excessive unloading of ventricle by device Arrhythmias	Bolus fluids Lower pump speed Treat arrhythmias

#### Algorithm for Selection of LVAD Candidates



## LVAD Implant Evaluation

#### **Tests**

- Abdominal ultrasound
- ABI measurements
- Carotid dopplers
- EGD or colonoscopy
- Panorex
- CT chest, abdomen, pelvis
- CXR PA & lateral
- 12-lead EKG
- Echocardiogram
- Cardiac catheterization
- Transplant psychology

#### Labs

- Basic chem
- CBC with differential
- Albumin, prealbumin
- Iron, ferritin, transferrin
- Thyroid panel
- LFT's
- Lipid panel
- HgA1c
- HIV, Hep B, Hep C

#### **INTERMACS Classification**

INTERMACS Profile	Description	Time Frame for Intervention
Profile 1	Critical cardiogenic shock	Definitive intervention needed within <i>hours</i>
Profile 2	Progressive decline	Definitive intervention needed within few days
Profile 3	Stable but inotrope dependent	Definitive intervention elective over a period of <i>weeks to few months</i>
Profile 4	Resting symptoms	Definitive intervention elective over a period of <i>weeks to few months</i>
Profile 5	Exertion intolerant	Variable urgency, depends upon maintenance of organ function & activity
Profile 6	Exertion limited	Variable, depends upon maintenance of organ function & activity
Profile 7	Advanced NYHA III	Transplantation or MCS may not currently be indicated

#### LVAD Indications

- Bridge to transplantation (BTT)
- Destination therapy (DT)
- Bridge to candidacy (BTC) / Bridge to decision (BTD)
- Bridge to recovery (BTR)

# Criteria for Consideration of LVAD for DT

- Not a transplant candidate
- LVEF < 25%</li>
- Peak oxygen consumption (VO<sub>2</sub>) < 14 ml/kg/min or < 50% predicted</li>
- 1. NYHA class IIIb or IV heart failure symptoms for at least 45 days of 60 days despite best medical therapy, **or**
- 2. IABP for dependent for 7 days, or
- 3. Inotrope dependent for 14 days

#### Increase in DT

Table 5 CF-LVA	D/BiVAD Imp	lants: June	2006 to	December 2013	(N = 9,372)
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	Implant date era						
	2008-2010		2011-2013				
Device strategy at time of implant	n	%	n	%			
BTT listed	1,133	39.0%	1,342	26.4%			
BTT likely	765	26.3%	1,387	21.5%			
BTT moderate	296	10.2%	663	10.3%			
BTT unlikely	82	2.8%	218	0.75%			
DT	591	20.3%	2,781	43.0%			
BTR	15	1.0%	31	1.0%			
Rescue therapy	10	0.3%	17	0.3%			
Other	14	0.5%	26	0.4%			
Total	2,906	100.0%	6,465	100.0%			

CF, continuous flow.

#### LVAD Contraindications

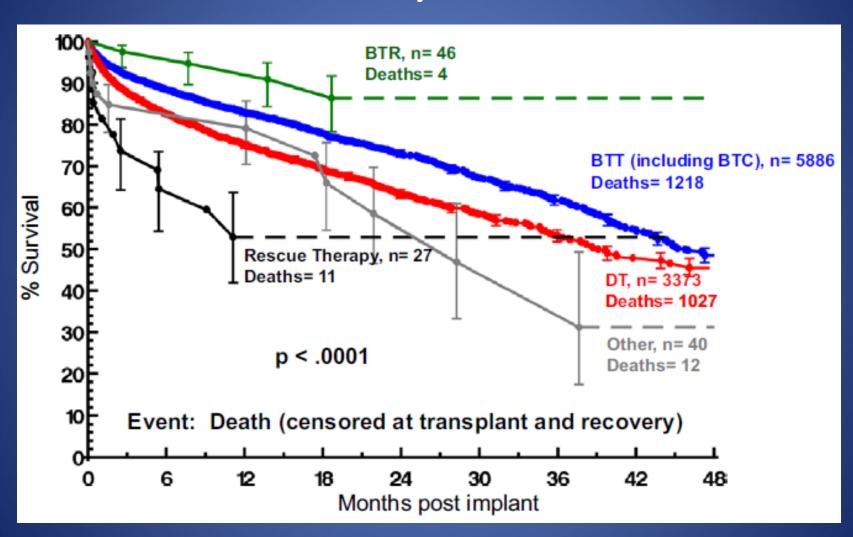
#### Relative

- Age > 65 years
- CKD with Scr > 3 mg/dL
- Severe chronic malnutrition
  - Males:  $BMI < 21 \text{ kg/m}^2$
  - Females: BMI < 19 kg/m²</p>
- Morbid obesity
  - BMI > 40 kg/m<sup>2</sup>
- Mechanical ventilation
- Severe mitral stenosis or uncorrectable regurgitation
- Moderate to severe aortic insufficiency

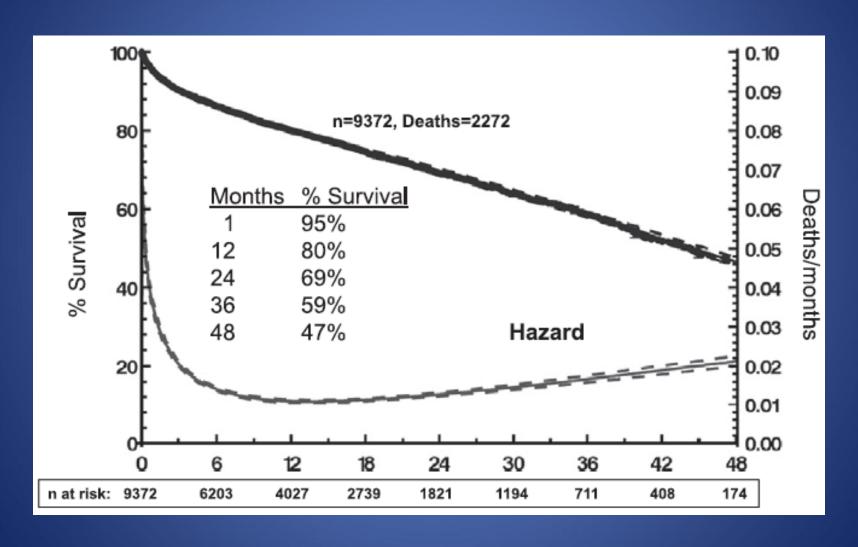
#### **Absolute**

- Potentially reversible cause of HF
- High surgical risk
- Recent or evolving stroke
- Neurologic deficits that impair managing the VAD
- Coexisting terminal illness
- AAA ≥ 5 cm
- Active systemic infection
- Inability to tolerate anticoagulation
- Severe pulmonary dysfunction
- Impending renal or hepatic failure
- Significant psychosocial support issues that may impair the ability to maintain and operate the VAD

# Survival by Indication



#### **CF LVAD Survival Data**



## Common Post-Op Complications

- Bleeding
- Cardiac tamponade
- Infection
- Arrhythmia
- Hemodynamic compromise
- Hypovolemia
- Right heart failure
- Neurologic complications
- Hemolysis
- Thromboembolism
- Organ dysfunction
- Depression
- Psychosocial issues

#### Peri- & Post-op Anti-infectives

- The optimal regimen is unknown
- Antibiotic past 48 hours is probably unnecessary
  - Until chests tubes removed
  - Delayed chest closure
- Guidelines refer to the REMATCH trial regimen
  - Vancomycin, rifampin, levofloxacin, & fluconazole

# Peri- & Post-op Anti-infectives

What is the optimum antibiotic prophylaxis in patients undergoing implantation of a left ventricular assist device?

Metesh Nalin Acharyaa\*, Robin Soma and Steven Tsuib

- Reviewed 10 best evidence papers
- Many confounders
- Concluded:
  - Beta-lactam for primary prophylaxis
  - Supplemented by vancomycin where MRSA is suspected
  - Limited duration antifungal may benefit some groups
  - Topical mupirocin is recommended
  - Duration 48-72 hours post-op

# Treatment of Bleeding in Post-op VAD Implant Setting

- Lacking a clear definition
- Use multi-pronged treatment approach
- Identify all contributing factors
- Differentiate surgical or anatomical bleeding from coagulopathic bleeding
  - location(s), laboratory values
- Withhold / reverse medications that may be contributing
- Replace what is missing or defective
  - pRBC's, platelets, FFP, cryoprecipitate, factor concentrates

#### Post-op Antithrombotic Strategy HMII

Timing	Action	Target
After CPB	Complete reversal of heparin	NA
ICU admission - 24 hours	No action required, consider ASA	NA
POD 1-2 with other indication for anticoag	IV heparin or alternative if no signs of bleeding ASA 81-325	PTT 40-60 seconds
POD 2-3 with other indication for anticoag	IV heparin Warfarin ASA 81-325 mg	PTT 60-75 seconds INR per indication
POD 2-3 no other indication for anticoag	Warfarin ASA 81-325 mg	INR 2-3 (1.5-2.5)

J Heart Lung Transplant. 2009;28:881-887. J Thorac Cardiovasc Surg. 2008;136:1318-1323. J Heart Lung Transplant. 2010;29:616-624. J Heart Lung Transplant. 2013;32:157-187.

#### Post-op Antithrombotic Strategy HVAD

Timing	Action	Target	
After CPB	Complete reversal of heparin	NA	
ICU admission - 24 hours	No action required, consider ASA	NA	
POD 1-2	IV heparin or alternative if no signs of bleeding* ASA 81-325	PTT 40-60 seconds	
POD 2-3	IV heparin Warfarin ASA 81-325 mg	PTT 60-80 seconds INR 2-3	

<sup>\*</sup>chest tube drainage should be less than 40 ml/hr for approximately three hours before starting anticoagulation, and H&H stable

#### Neurologic Events

- Multiple mechanisms
- Possible predictors
  - History of stroke
  - Post-operative infection

Intention	Dest	tination therapy	Bridge-to-Transplant					
Device	Н	leartMateII <sup>80</sup>	HeartWare HeartMateII <sup>77</sup>					
(n)	133			140			281	
Pt/yrs		211		87			181.8	
	%	Event/pt-yr	%	Event/pt-yr	%	Event/pt-yr	0-30 days	> 30 days
Ischemic	8	0.06	7.1	0.11	5	0.09	0.37	0.05
Hemorrhagic	11	0.07	2.9	0.05	3	0.05	0.18	0.03
TIA			5.0	0.08	2	0.04	0.14	0.02
Other neuro	22	0.17			5	0.09	0.18	0.08

Management strategy varies significantly

#### **Blood Pressure**

- Best measured by invasive arterial catheter
  - Doppler (alternative)

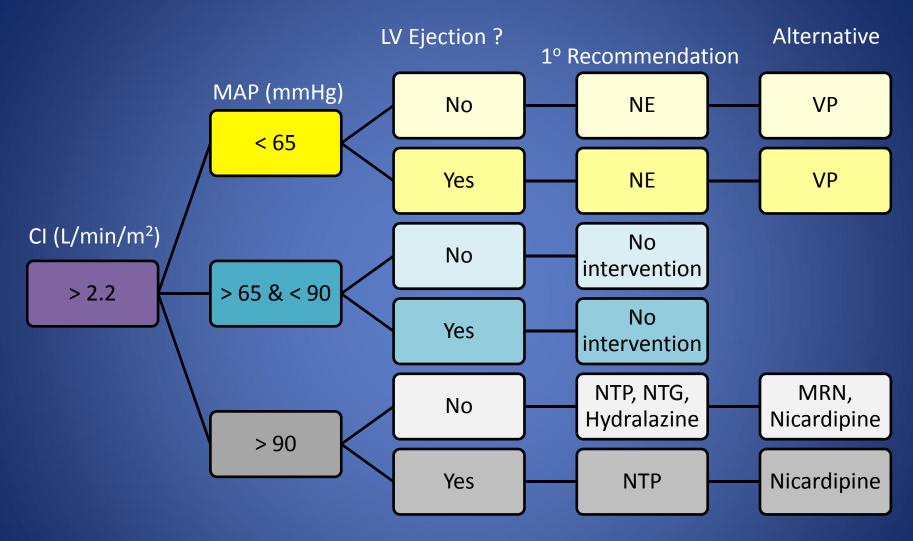
Narrow pulse pressure, typically 5-25 mmHg

- Mean arterial pressure (MAP)
  - Target: 60-80 mmHg, shouldn't exceed 90 mmHg

## Approach to High MAP

- Elevated MAP can:
  - Reduce forward flow
  - Elevate stroke risk
- Vasodilators and afterload reducing agents
  - Nitroprusside
  - Nicardipine
  - Nitroglycerin
  - Hydralazine
  - Eventual resumption of ACEi or ARB

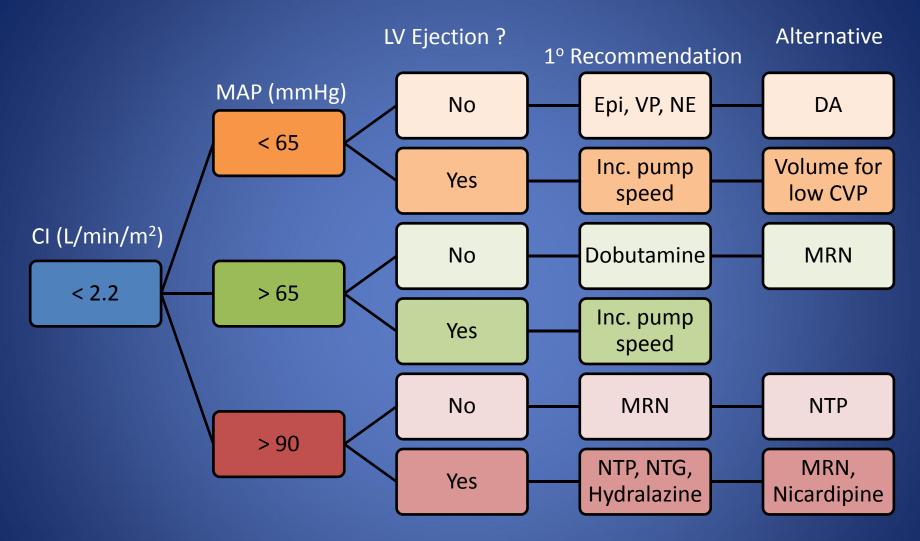
#### Approach to Post-op Hemodynamics



CI, cardiac index; MAP, mean arterial pressure; LV, left ventricular; VP, vasopressin; NE, norepinephrine; MRN, milrinone; NTP, nitroprusside; NTG, nitroglycerin

J Heart Lung Transplant. 2013;32:157-187. Crit Care Med. 2014;42:158-168.

#### Approach to Post-op Hemodynamics



CI, cardiac index; MAP, mean arterial pressure; LV, left ventricular; Epi, epinephrine; VP, vasopressin; NE, norepinephrine; DA, dopamine; CVP, central venous pressure; MRN, milrinone; NTP, nitroprusside; NTG, nitroglycerin

#### Approach to Low Pump Output

(not speed related)

#### Evaluate: CVP, PAP, PAOP, MAP and Echo

CVP	$\downarrow$	<b>↑</b>	<b>↑</b>	<b>↑</b>	<b>↑</b>
PAP	$\rightarrow$	$\rightarrow$	$\uparrow$ or $\leftrightarrow$	<b>↑</b>	<b>↑</b>
PAOP	$\rightarrow$	$\rightarrow$	$\downarrow$	<b>↑</b>	<b>↑</b>
MAP	$\rightarrow$	$\rightarrow$	<b>→</b>	$\downarrow$	<b>→</b>
Echo	Under filled	Signs of RV compression	RA/RV dilated	LA/LV dilated AV opening Inflow malposition	LA/LV dilated AV opening
Diagnosis	Hypovolemia or Obstruction	Tamponade	Right heart failure	Inflow obstruction (rare)	Outflow obstruction (very rare)

## Hypovolemia Management

- May experience suction events or decrease pulsatility
- Hemoglobin < 10 mg/dL</li>
  - Transfuse pRPBC's (leukopoor)
- Ongoing bleeding: consider balanced approach to hemostasis
  - 1:1:1 transfusion (pRBCs:FFP:PLTs)
- Hemoglobin > 10 mg/dL
  - Colloid: 12.5-25 grams (250-500 mL) albumin 5%
  - Crystalloid: 250-500 mL Plasma-Lyte
- Monitor flow, CVP, MAP

## Right Ventricular Failure (RVF)

- Lacking a standard definition:
  - Signs and symptoms
  - -CVP > 16 mmHg
- Severity: scaled by intervention and duration
- Incidence: 20-50%
- Risk factors:
  - Gender
  - Pulmonary vascular disease
  - End-organ dysfunction

## Management of RVF in LVAD's

- Medical management
  - PAC-guided optimization of hemodynamics and fluids
  - Pulmonary vasodilators
  - Inotropes
- Surgical Management
  - Repair mod-severe TR?
  - Temporary RVAD
  - TEE-guided pump adjustments

Best Pract Res Clin Anaesthesiol. 2012;26:217-229. Pharmacotherapy. 2010;30:728-740. Heart Vessels. 2002;13:69-71. Artif Organs. 2014;38:963-967. Circ Heart Fail. 2008;1:213-219.

#### Further Complications in the LVAD Patient

- Post discharge
- Most frequent causes of admission



**VERSUS** 

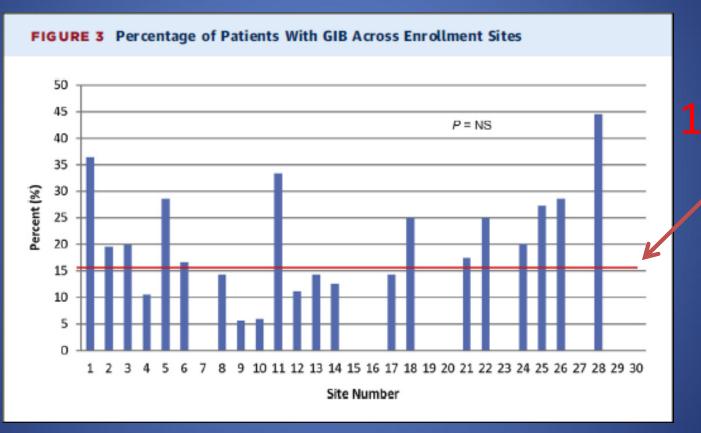


Bleed

## GI Bleeding

Table 1 Contemporary studies showing incidence of GIB after HeartMate II implantation (11,14-18)						
Study author	Number of patients receiving LVAD	Device implanted	GI bleed incidence (%)	Notes		
Morgan et al. (14)	86	HeartMate II	22.1	No mortalities associated with GIB, transfused average 3.8±1.3 units PRBCs, median length of stay 10 days.		
Stern et al. (15)	33	HeartMate II	40	No source identified in 65% of episodes of GIB.		
Demirozu et al. (16)	172	HeartMate II	19	All cases managed medically.		
Kushnir et al. (18)	154	HeartMate II	18.8	Transfused 3.0 units PRBCs per bleeding event, 70% source found with endoscopy.		
Aggarwal et al. (17)	101	HeartMate II	22.8	57% upper GI source. One mortality associated with GIB.		
John et al. (11)	130	HeartMate II	17.6			
GIB, gastrointestinal bleeding; LVAD, left ventricular assist de						

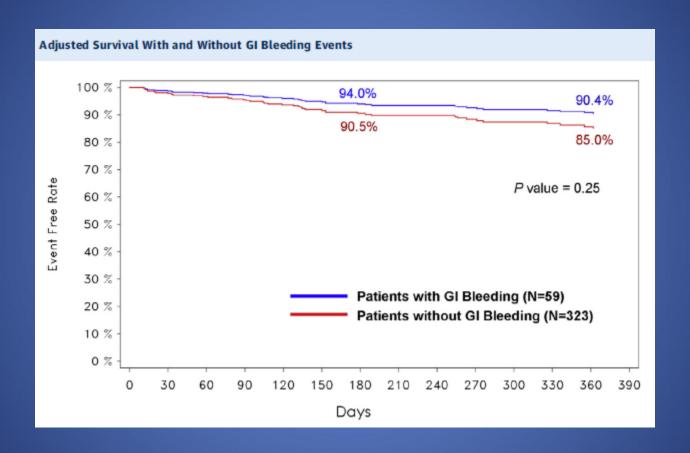
## GI Bleeding



15.4%

*J Am Coll Cardiol HF.* 2015;3:303–13.

### GI Bleed - Outcomes



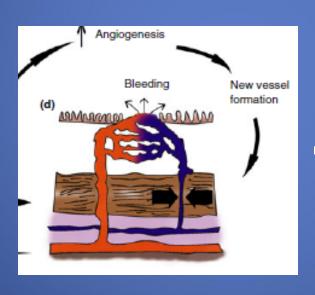
## GI bleeding: Mechanisms

- Multifactorial!
  - Anti-thrombotic regimens
    - Warfarin, aspirin
  - Acquired Von Willebrand Syndrome
    - Aortic Stenosis Heyde Syndrome
    - Consistent with axial and centrifugal CF-LVAD devices
  - Continuous Flow
    - Narrow/low pulse pressure
    - Intestinal hypoperfusion/hypoxia
    - Dilation and Angiodysplasia

Ann Cardiothorac Surg. 2014;3(5):475-479.

## GI bleeding: Mechanisms



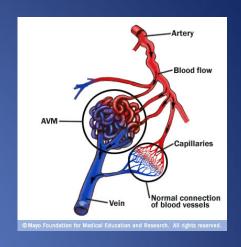


- Anticoagulation
- Platelet dysfunction
- Vasodilation
- Angiogenesis (VEGF)

= Arterial-Venous
Malformations (AVM's),
bleeding

#### Treatment

- Supportive Care
- Non-pharmacologic
  - Increase the pulse pressure
  - Cauterization/clip/epinephrine/argon plasma
  - VAD exchange/transplant
    - LVAD GI bleeding resolves with removal of continuous flow



## Pharmacologic options

- Reduction of Anti-thrombotic regimen
  - Reduce/hold aspirin (vWF deficiency)
  - Reduce INR goal, hold or discontinue warfarin (2-4 weeks vs. indefinite)
- Octreotide
  - Short/long acting
  - Reduced blood transfusions and admissions

Table 1. Suggested Dosing and Administration of Octreotide for Gastrointestinal Bleeding in Patients with  Continuous-Flow Ventricular Assist Devices					
Formulation	Route	Dose	Frequency		
Injection solution (Sandostatin→) Microspheres for suspension, depot (Sandostatin long-acting release→)	Subcutaneous, intravenous Intramuscular	100 μg 20 mg	2–3 times daily Monthly		

Clin Cardiol. 2013. 36,4. 190-200. ASAIO Journal.2013; 59:450-451. J Cardiothorac Vasc Anesth. 2013;27(5): 939-43. J Heart Lung Transplant. 2015;34: 132-34.

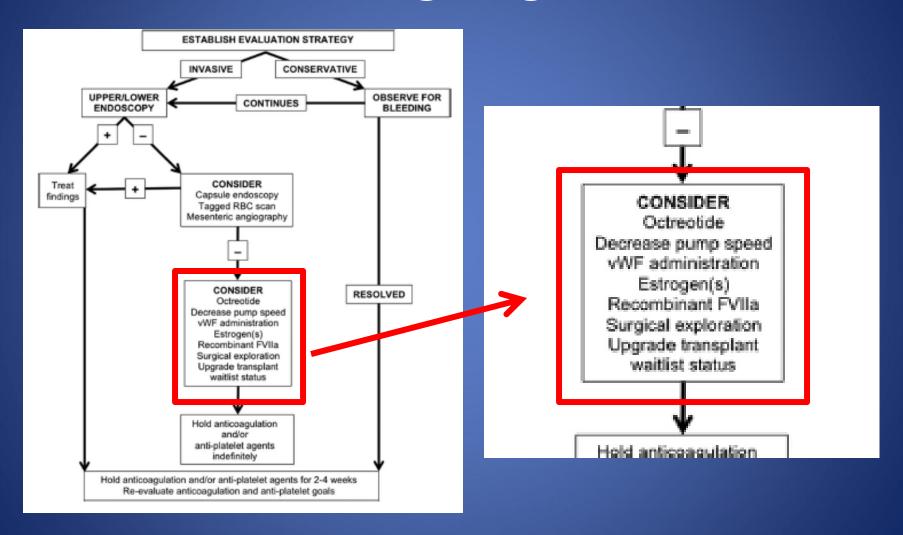
#### Thalidomide

- Decrease recurrence of bleeding
- Supported option in angiodysplasia literature
- Case report of success in VAD literature
- Access, REMS, pregnancy, hepatotoxicity
- 50mg every other day-100mg twice daily
- Hormonal therapy
  - Resolution of bleeding & and transfusions
  - No role in angiodysplasia literature
  - Case report of success in VAD literature

Ethynilestradiol 0.05 mg and norethindrone	26	Significantly reduced transfusion requirements over 6
1 mg		months $(p = 0.002)$
Norethynodrel 5 mg and mestranol 75 μg <sup>†</sup>	43	All patients treated with combination estrogen and
		progesterone had no further bleeding episodes*

(From AVM literature, not VAD)

## GI bleeding: Algorithm



Circulation. 2012;125:3038-3047.)

#### REVIEWS OF THERAPEUTICS

Thrombosis in Continuous-Flow Left Ventricular Assist Devices: Pathophysiology, Prevention, and Pharmacologic Management

Douglas L. Jennings, <sup>1,2,\*</sup> and Phillip A. Weeks<sup>3</sup>

<sup>1</sup>Nova Southeastern University, Ft. Lauderdale, Florida; <sup>2</sup>Jackson Memorial Hospital/Miami Transplant Institute, Miami, Florida; <sup>3</sup>Memorial Hermann – Texas Medical Center, Houston, Texas

# Transitions of Care for the LVAD recipient

- Pharmacotherapy Role = Pharmacist Role
  - Maintenance
  - Complications
  - Many comorbidities
    - Advanced Heart Failure patient
    - Medication expertise beyond heart failure

## Unmet needs?





#### **ISHLT** statements

- LVAD Guidelines 2010
  - Class I recommendation for pharmacist as part of team
  - Inpatient recommendation
    - Medications continue as outpatient, correct?
    - Much education/confusion possible when transition to home

## JHLT Editorial recognition

- "LVAD patients present significant and unique medication challenges given the typical polypharmacy and their volatile physiology, which lead to frequent prescription changes."
- "We propose that the same level of education and adherence ascertainment should be enforced for those patients with mechanical devices ... similar to that mandated for organ transplant patients."

### Transitions Checklist

- Medication reconciliation
- Anti-thrombotic therapies (individualization)
  - Bridging needs
  - Beware of acute reversal
- Antimicrobials
- MAP control
- GI Prophylaxis

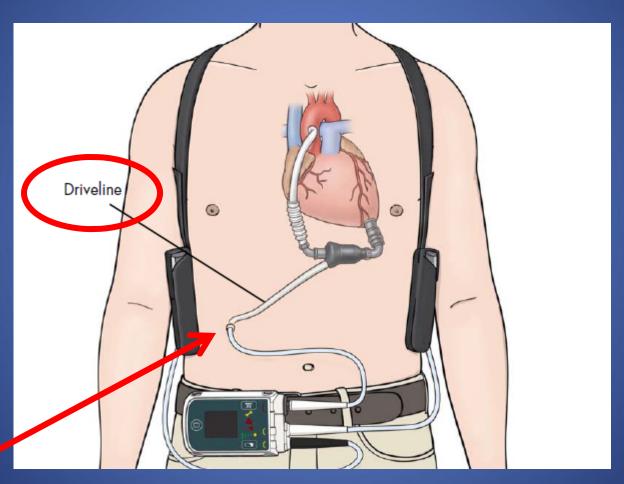
#### **MAP Control**

- Goal MAP 60-80 mmHg
- No medications with survival benefit
  - Survival is not a compelling indication
- Hypertension preferences (Class I, LOE C)
  - ACEi/ARB, BB, hydralazine/nitrates
  - Standard contraindications apply
  - Consider compliance-friendly regimens

## Gastrointestinal Prophylaxis

- GI bleed incidence discussed previously (20-40%)
  - Coagulopathy, unique continuous flow risk
- Stress ulcer incidence in ICU (1-39%)
  - Prophylaxis warranted with risk factors
- Mechanisms related Hypoxia
- Preference toward H2RA vs. PPI?
  - PPI if history of GERD, GIB, gastritis, etc?
- Literature??

## Outpatient Challenges LVAD Driveline



Drive line • Exits body

Patient Handbood. HeartMate II Ventricular Assist System. Thoratec Corporation. 4/2013. www.thoratec.com. Accessed 4/2015.

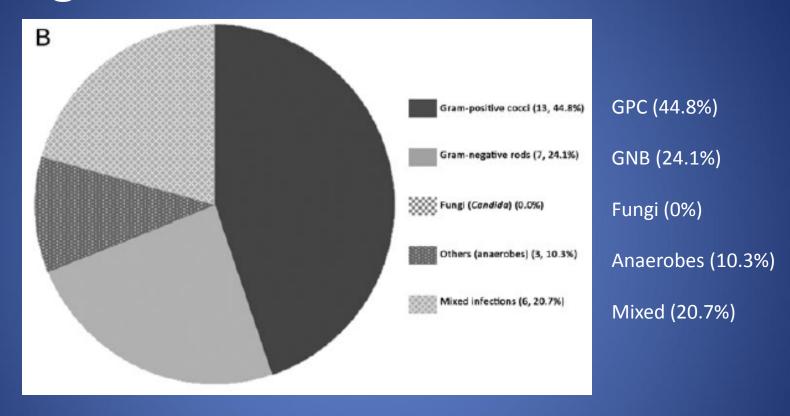
## CID study

- Retrospective review
- Three-center experience with CF-LVADs
- 247 patients
- Excluded patients implanted outside of the 3 centers involved

#### **Driveline Infection**

- Driveline infection was defined as infection involving the soft tissues surrounding the driveline exit site, typically accompanied by erythema, warmth, and purulent discharge.
- Incidence: 15% (15 cases/100 pt. LVAD years)
  - Most prevalent type of LVAD infection 47%
  - Common cause of other LVAD infection
  - Driveline trauma predictive of infection 100%
  - Median time to driveline infection 7.1 months
- Incidence 60-90% at 12 months other studies

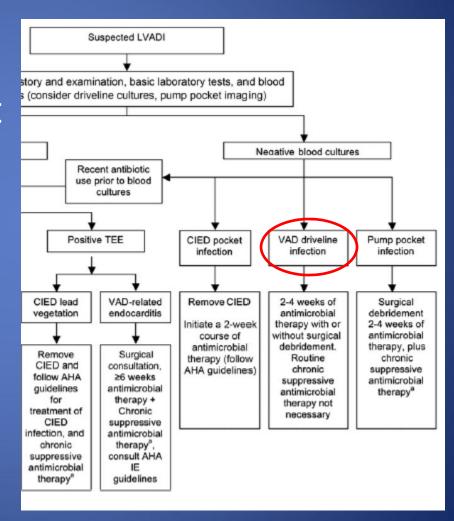
## Organisms – Driveline infection



- GPC: MSSA, MRSA, Enterococcus
- GNB: Nosocomial, PsAr, Klebsiella, E.coli, Steno, Serratia

## Treatment approach - CID

- Blood cultures –
   critical decision point
- Oral regimens 10-24 days, median 14
- Recommend 2-4 weeks
- Generally no suppressive therapy



#### Prior to antibiotics

- Clinical diagnosis
- Consider swab/culture
  - Not necessarily for diagnosis
  - If recurrent infection
  - Blood cultures not routine
- LVAD coordinator/engineers
  - Education
  - Assess need for stabilizer devices
  - Frequent follow up

#### Antibiotic choice

- Skin flora primary culprits
- Tailor choice of antibiotic
  - institutional sensitivities
  - patient history
- Cephalosporin may be adequate for some
- More broad coverage for others considered

More extensive – admission, surgery and ID consults considered

## Suppressive antibiotics

- Likely not necessary for simple driveline infection
- Often considered for more invasive infection of driveline or pump pocket or blood stream infections
  - ID consultation

#### Final Thoughts ... Questions?



Please feel free to contact us:

joseph.rinka@cuw.edu & jon.godden@aurora.org