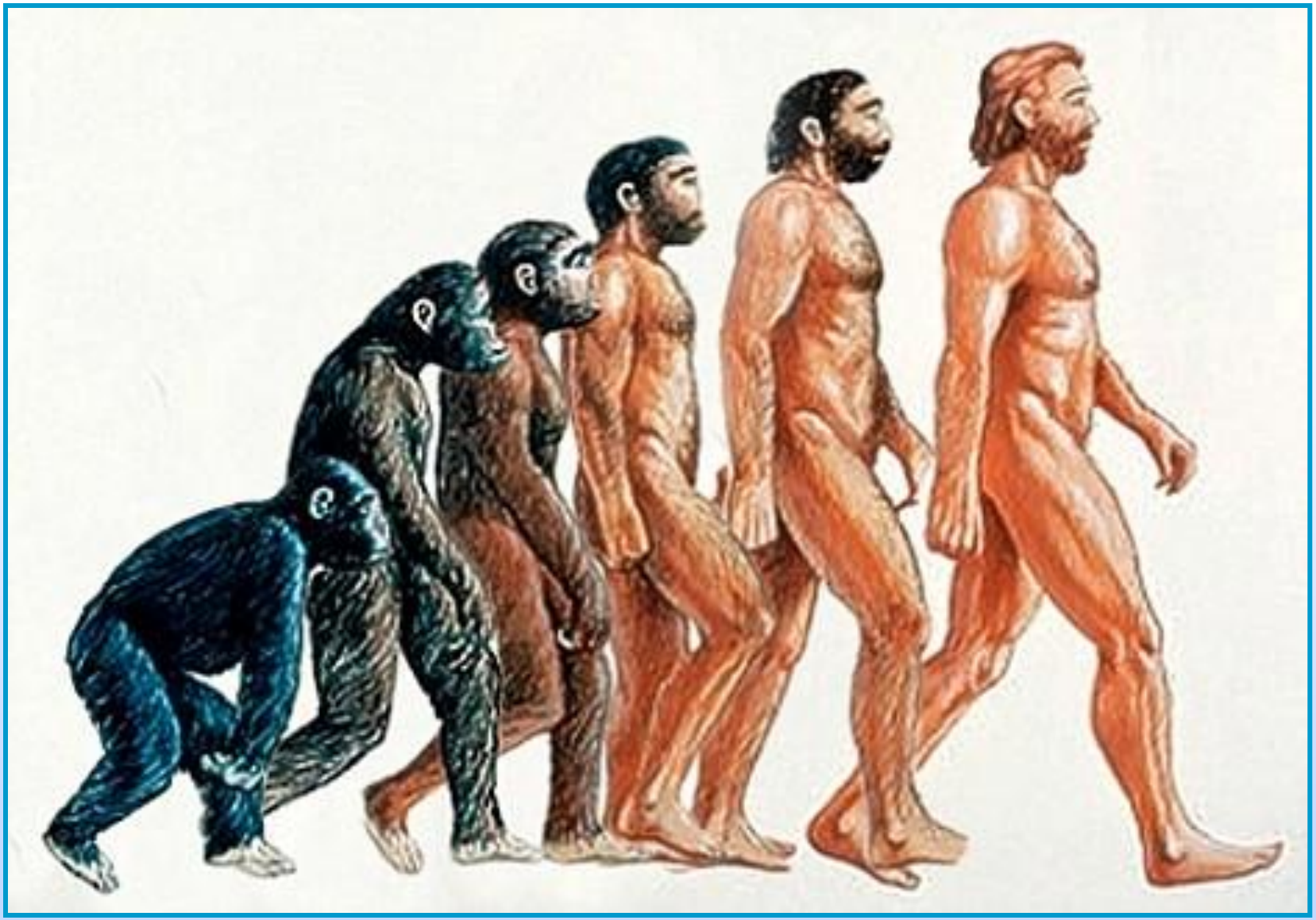
MAYO CLINIC

LVAD Therapy for End Stage HF
The Mayo Experience

Sudhir Kushwaha, MD

Medical Director
Cardiac Transplant and LVAD Program
Mayo Clinic



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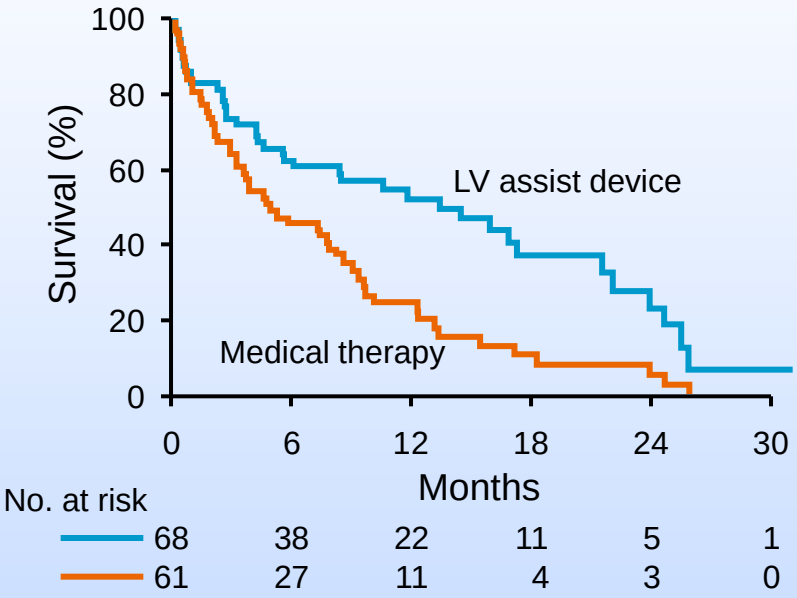
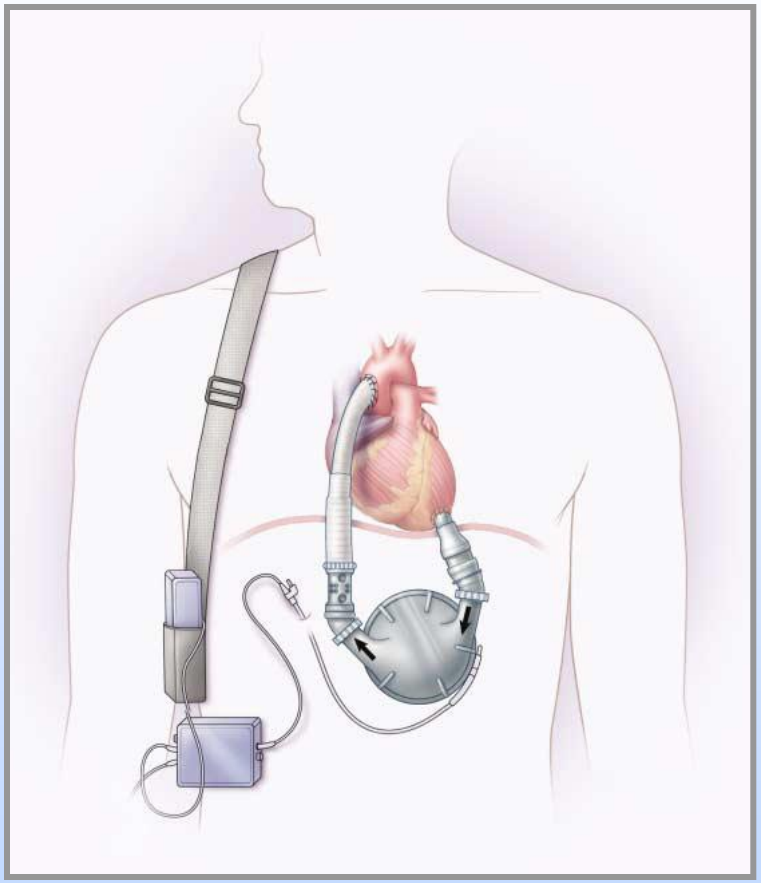
Pulsatile Pumps (REMATCH)





N Engl J Med Vol 345; No. 20 – November 15, 2001

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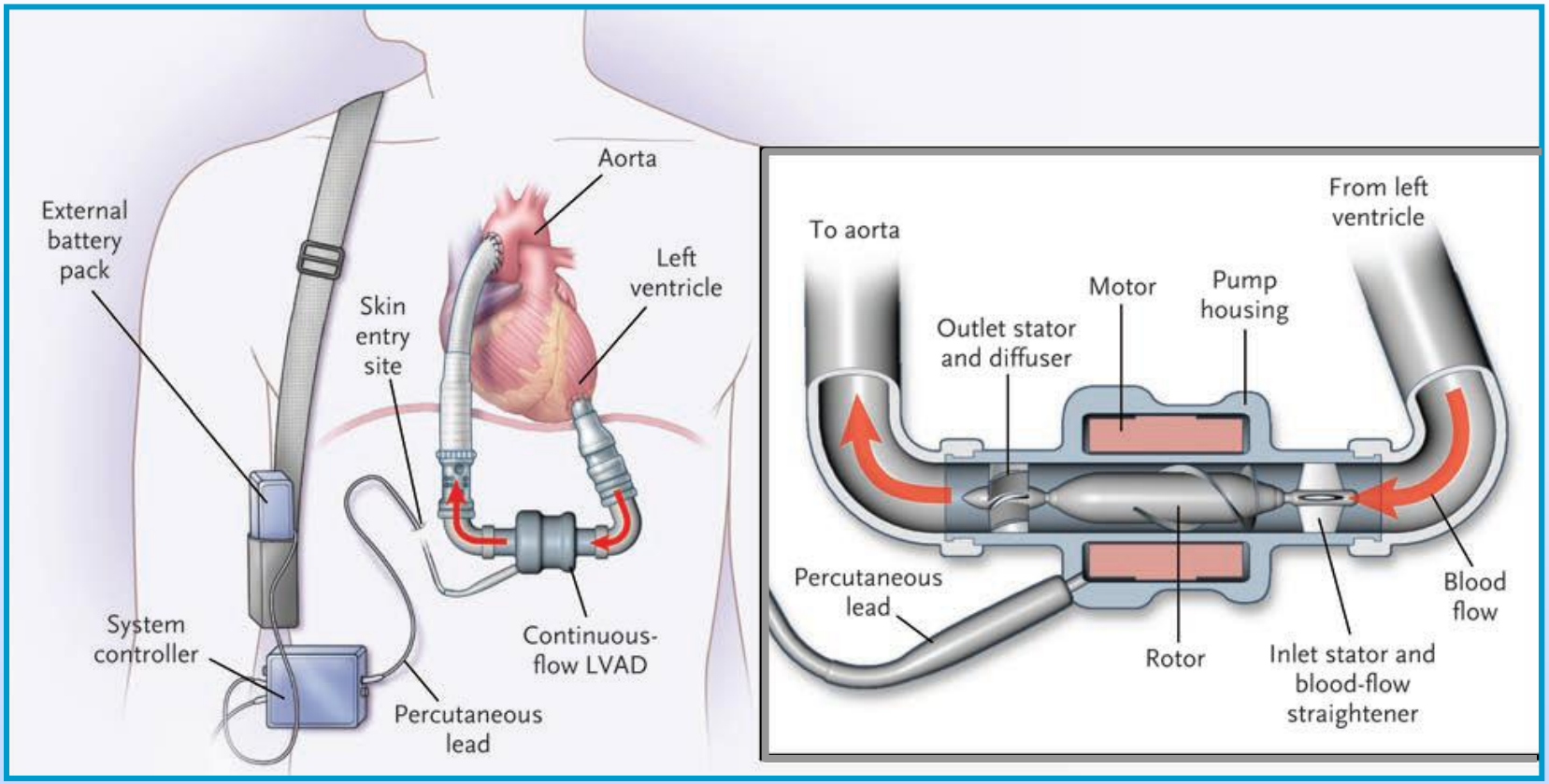
Axial Flow Pumps



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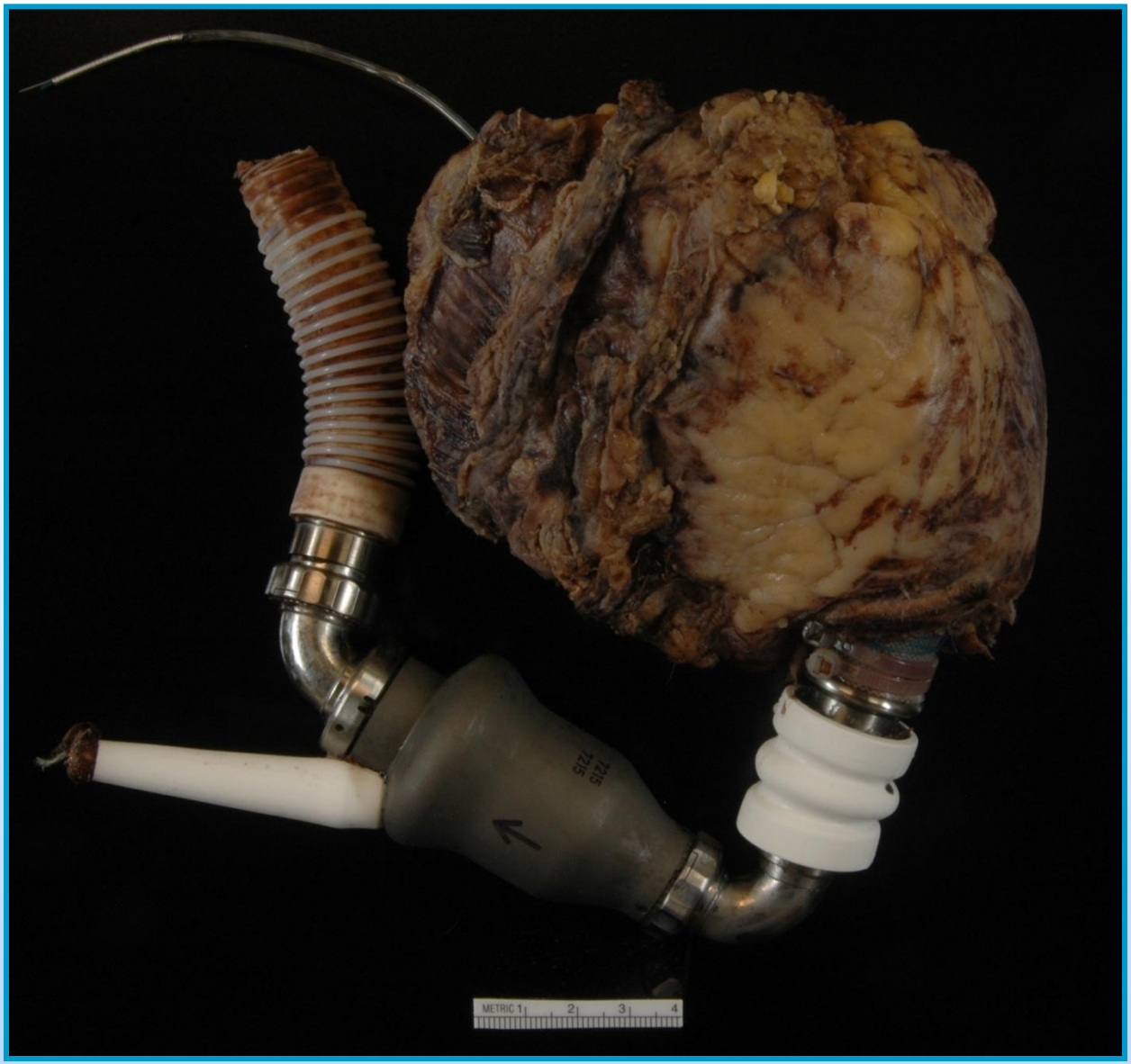

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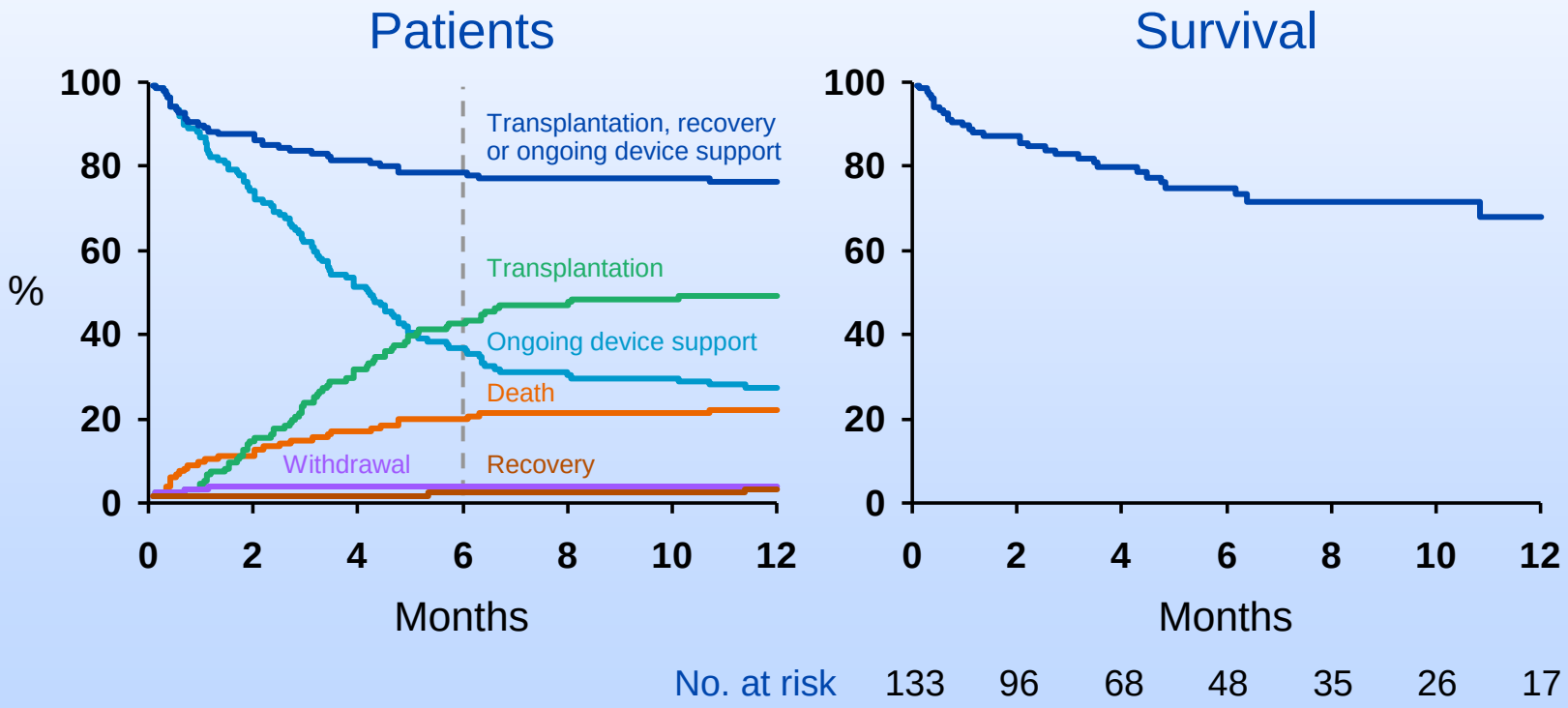
Survival Following Continuous Flow Pump as BTT

- HeartMate II investigational study group
- 133 patients



Miller: NEJM, 2007

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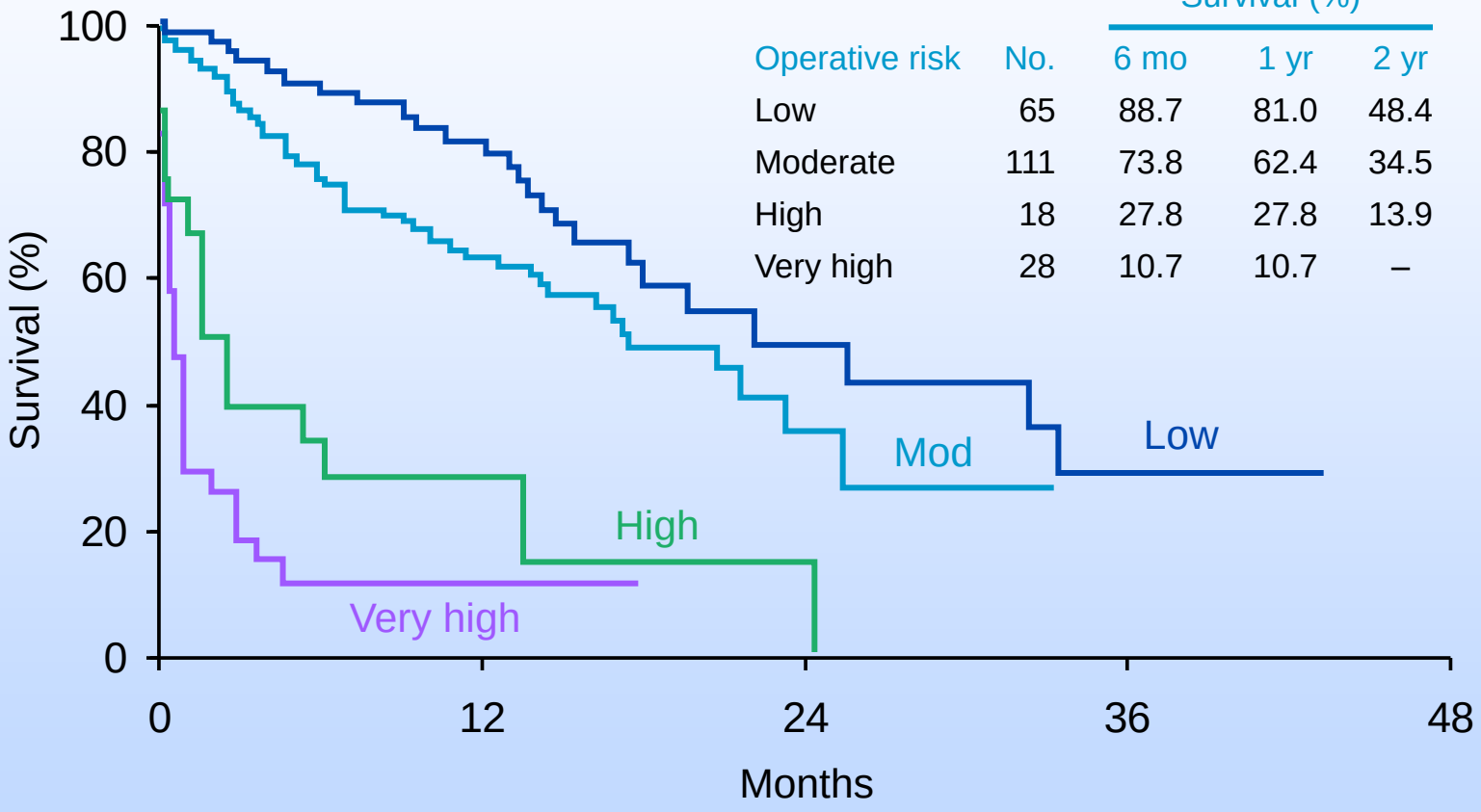
Survival After LVAD (HM-I) Implantation as DT by candidate's Operative Risk



Operative risk	No.	Survival (%) 6 mo	1 yr	2 yr
Low	65	88.7	81.0	48.4
Moderate	111	73.8	62.4	34.5
High	18	27.8	27.8	13.9
Very high	28	10.7	10.7	–

Lietz et al: Circ 116:497, 2007

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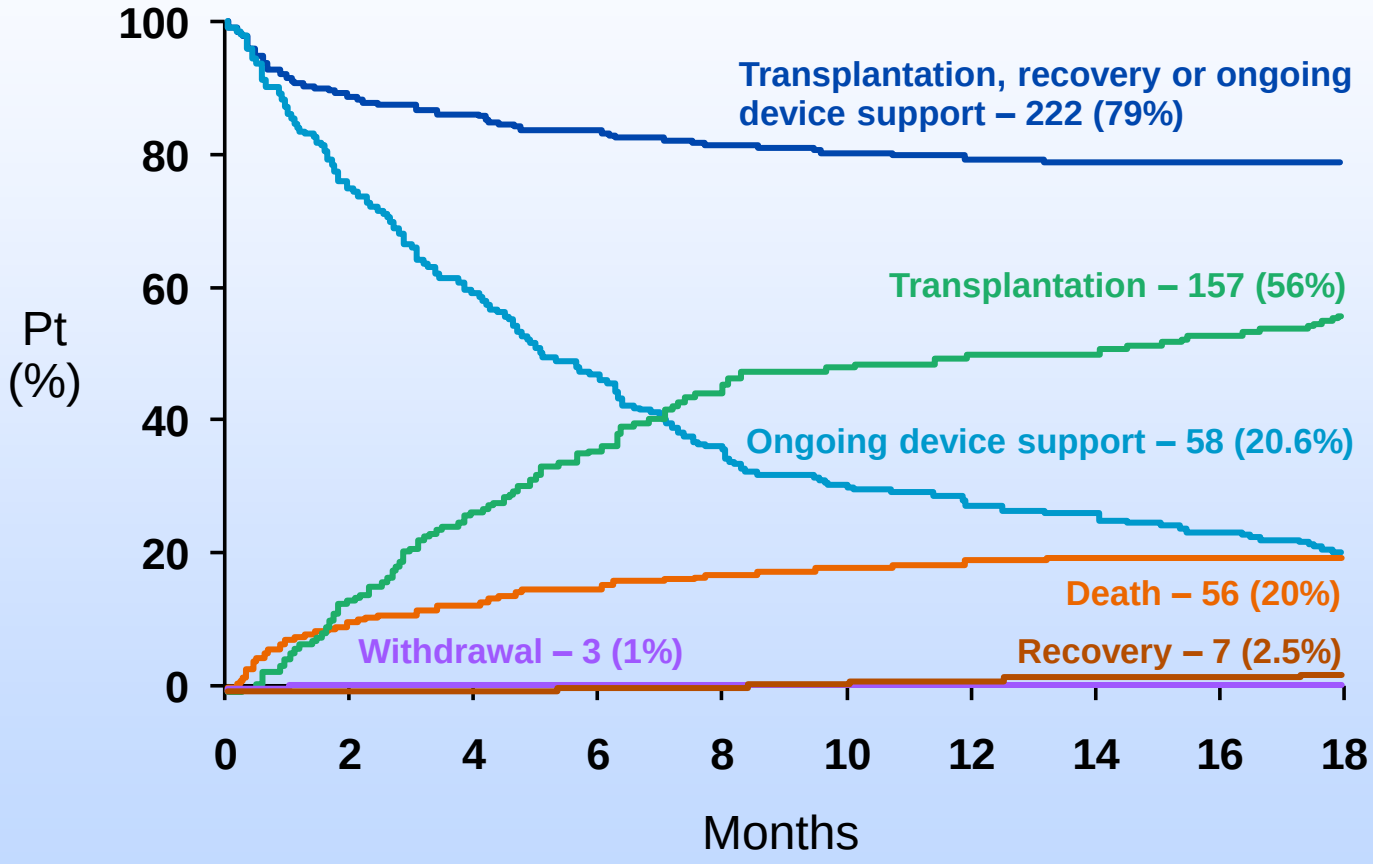
Extended Mechanical Circulatory Support with Continuous-Flow Rotary LV Assist Device



Pagani et al: JAAC 54, 2009

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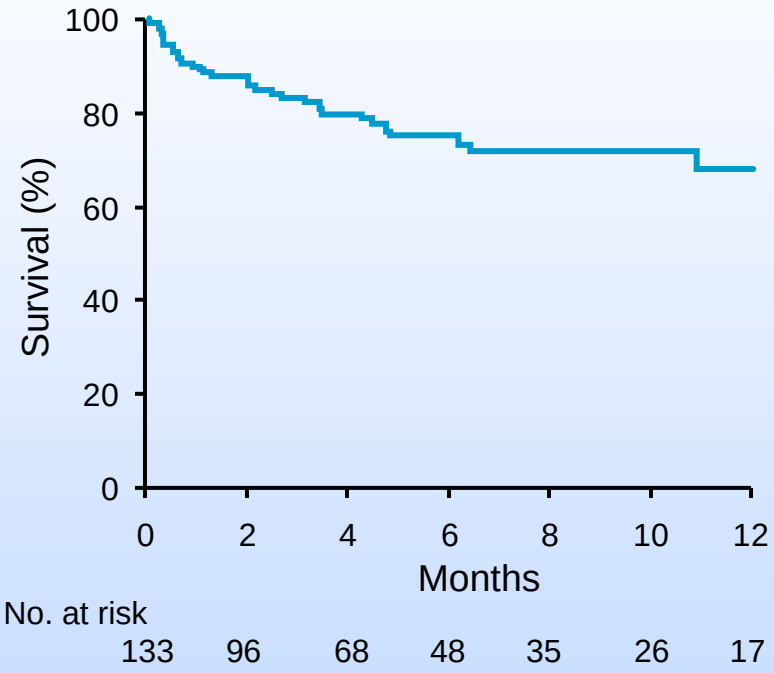
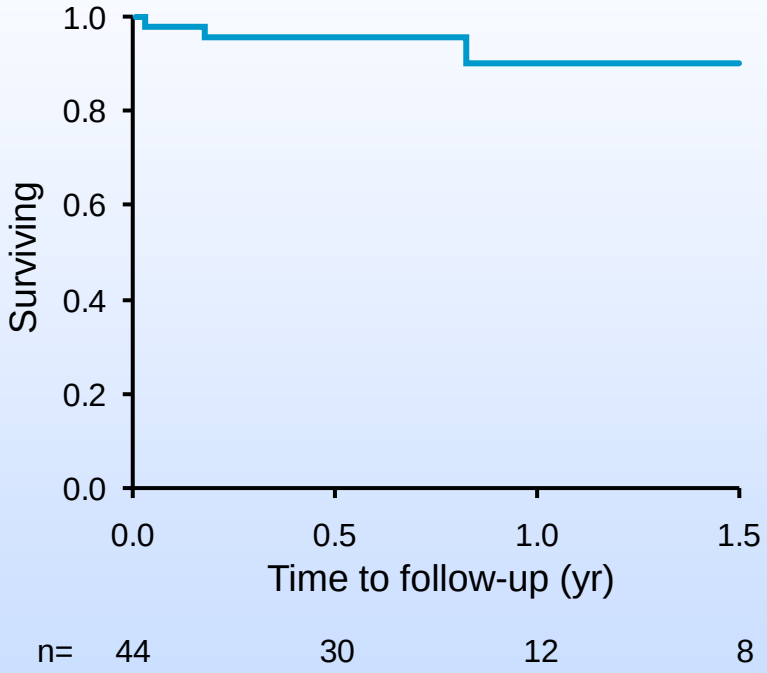
Survival (Bridge to Transplant)





N Engl J Med 357:9, 2007

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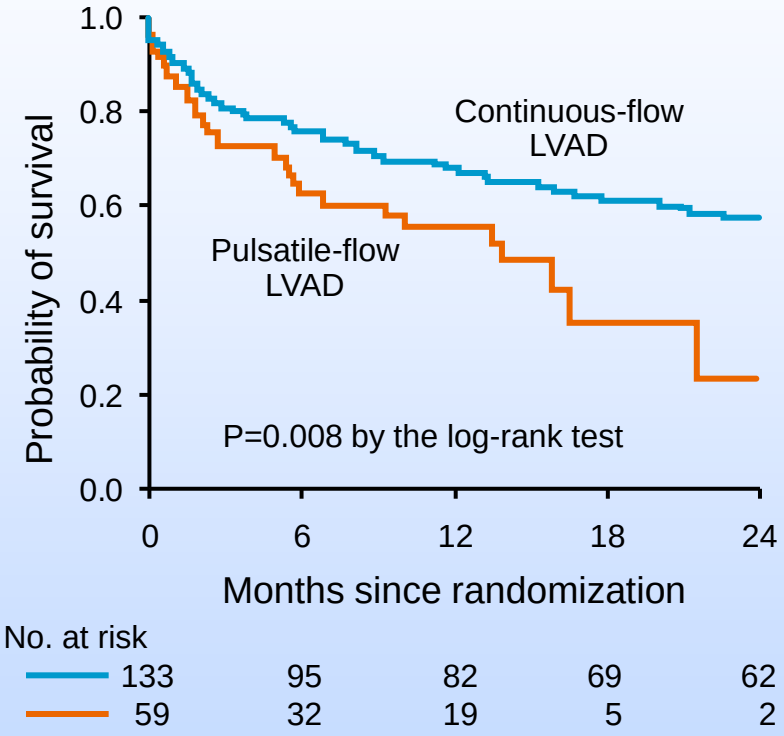
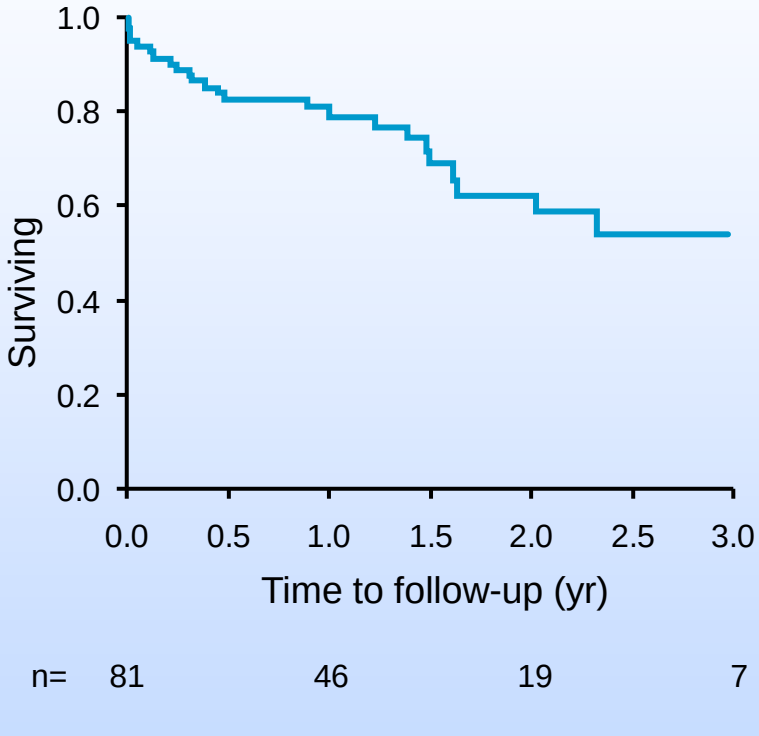
Survival (Destination Therapy)





N Engl J Med 361:23, 2009

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Causes of Death (56/281)

Cause of death	Pt (%) (n=281) No.	Deaths (%)	Implants (%)
Sepsis	11	20	4.0
Right heart failure	7	13	2.5
MOF	5	9	1.8
Ischemic stroke	5	9	1.8
Hemorrhagic stroke	5	9	1.8
Internal components (2 thrombosis, 1 elbow disconnect, 1 graft twisted)	4	7	1.4
External components (2 loss of power, 1 perc lead trauma)	3	5	1.1
Other	16	28	6.0

Pagani et al: JAAC 54, 2009

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Adverse Events from INTERMACS

June 2006-Dec 2007 (n=420)

Adverse event	<30 d events	Pt	>30 d events	Pt	Total events	Pt
Device malfunction	15	12	52	42	67	53
Bleeding	228	114	156	64	383	146
Cardiac/vascular						
Right heart failure	21	21	6	5	27	25
Myocardial infarction	1	1	0	0	1	1
Cardiac arrhythmia	92	62	35	22	127	77
Pericardial drainage	36	31	4	3	40	34
Hypertension	29	28	61	41	90	66
Arterial non-CNS thrombosis	9	7	5	5	14	12
Venous thrombotic event	16	14	7	6	23	18
Hemolysis	8	7	14	11	22	17
Infection	161	100	194	107	355	160
Neurologic dysfunction	61	51	39	33	100	77
Renal dysfunction	65	54	13	12	78	64
Hepatic dysfunction	31	27	24	18	55	41
Respiratory failure	93	74	17	14	110	84
Other						
Wound dehiscence	2	2	4	4	6	6
Psychiatric episode	14	14	37	28	51	38
Other adverse events	89	60	151	90	240	136
Total adverse events (prospective)	970,819		1,789		NA	

J Heart Lung Transplant 27:1065, 2008

MAYO CLINIC

Importance of a Multi-Disciplinary Approach

Cardiac surgery

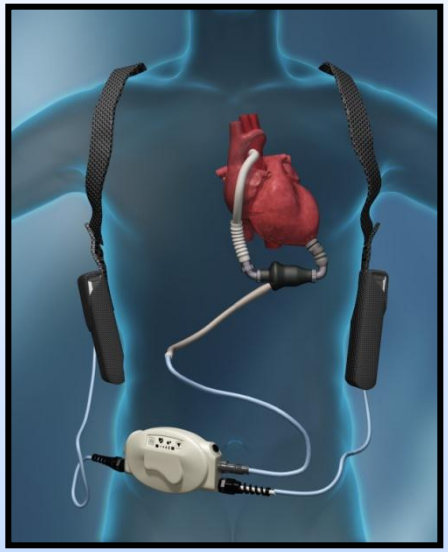
Cardiology

Coordinators

Nursing

Vascular medicine

Rehabilitation



Neurology

VAD Tec.

Physical t.

Hematology

Psychiatry

Social Work

Nephrology

Dietary service

Occupational t.

Gastroenterology

Insurance

Chest surgery

Pharmacy

Hepatology

Radiology

General surgery

Infectious disease

Urology

Rheumatology

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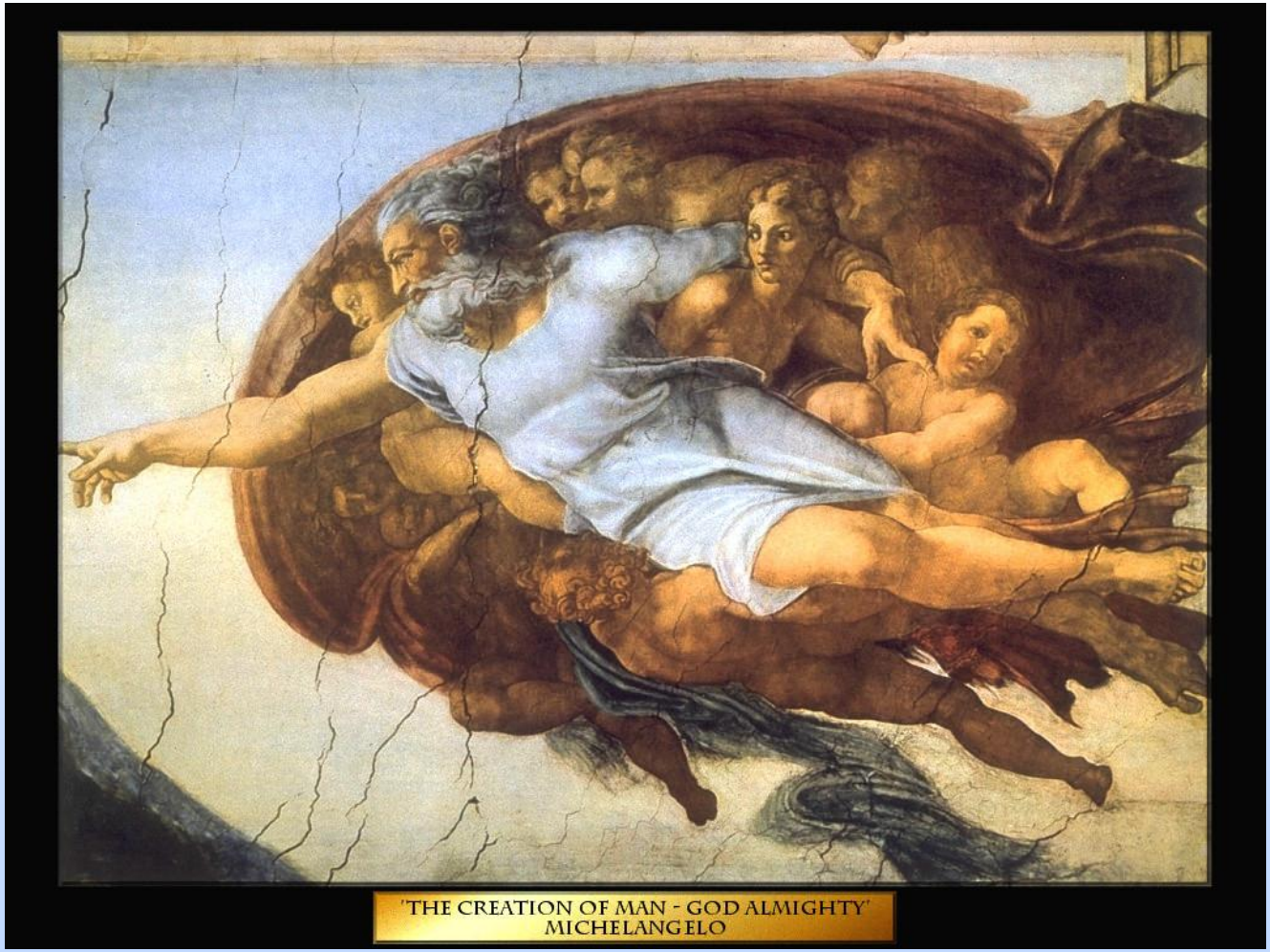
Cardiac Surgery



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Cardiac Surgery

- Valve disease (TR, AI, MR)
- Preserving RV function
- New frontiers (restrictive CM, hypertrophic CM, congenital)

Cardiology – Diagnostics

- Echo
  - Pre-op, intra-op, complications
  - Pump optimization
- Catheterization
  - Pump optimization (± exercise)
  - Recovery trial

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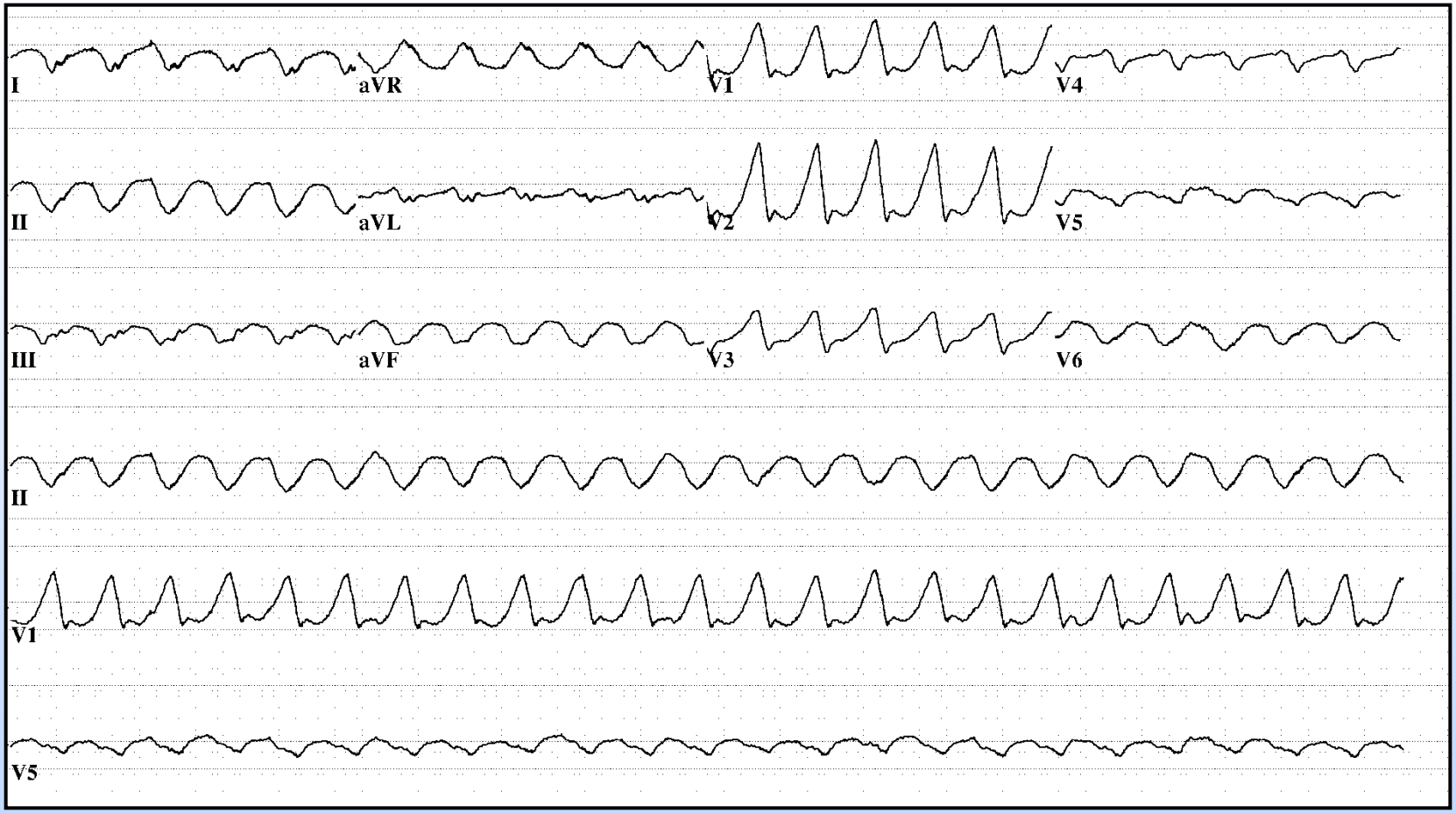
Cardiology – Arrhythmias



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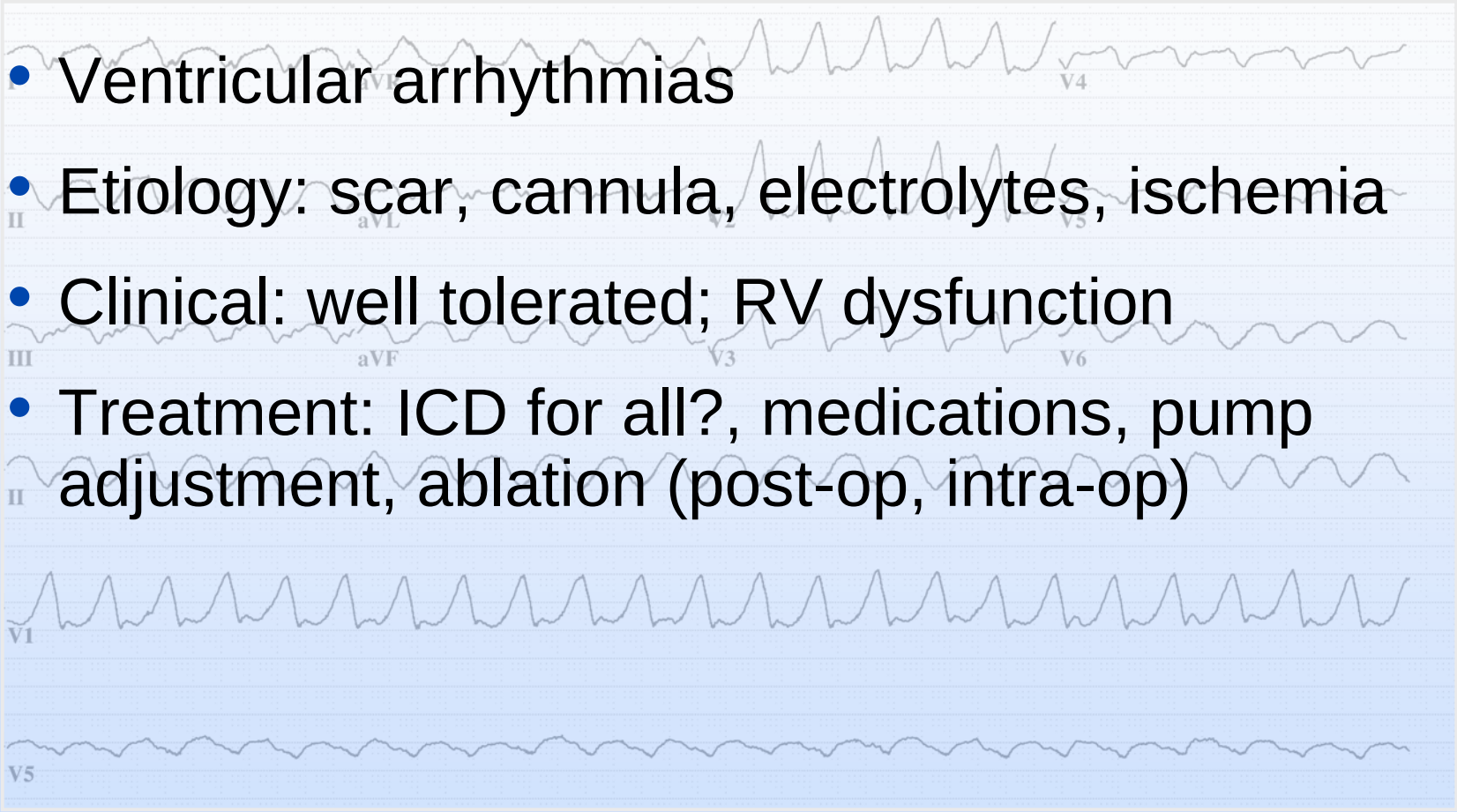
Cardiology – Arrhythmias

- Ventricular arrhythmias
- Etiology: scar, cannula, electrolytes, ischemia
- Clinical: well tolerated; RV dysfunction
- Treatment: ICD for all?, medications, pump adjustment, ablation (post-op, intra-op)



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Cardiology – Heart Failure Management

- Markers (BNP, Troponin)
- Medications

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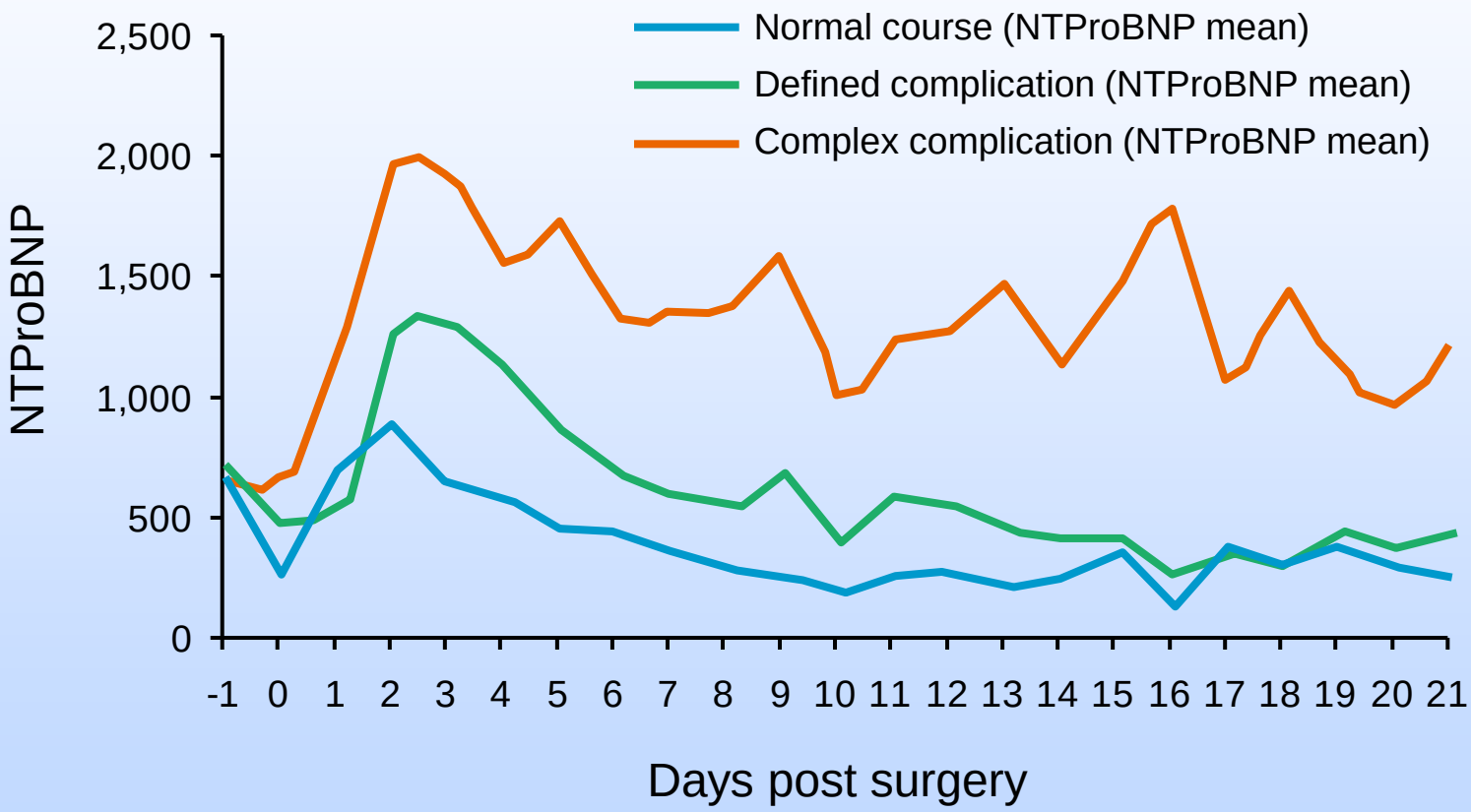
NTProBNP Levels After Surgery



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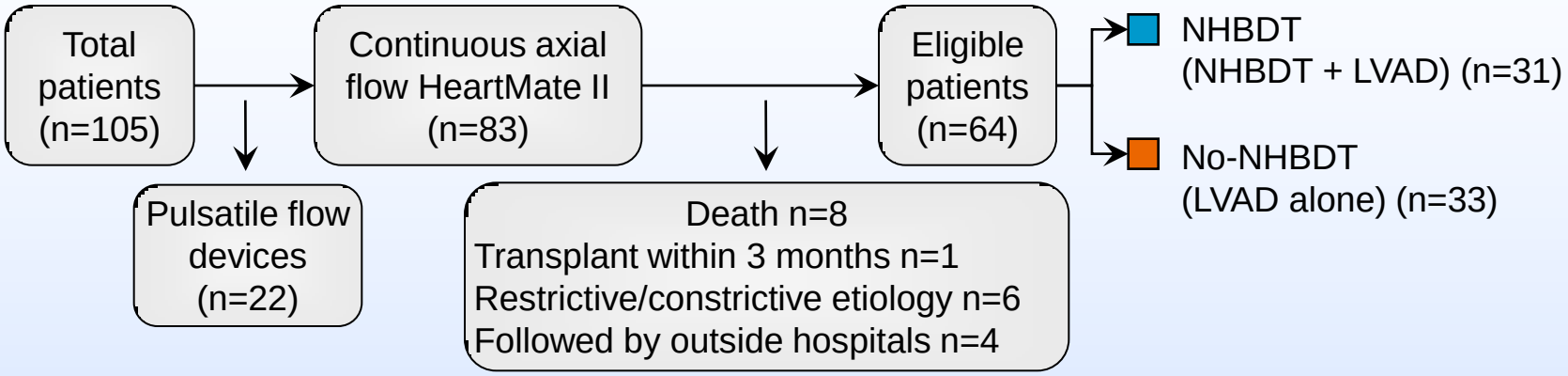
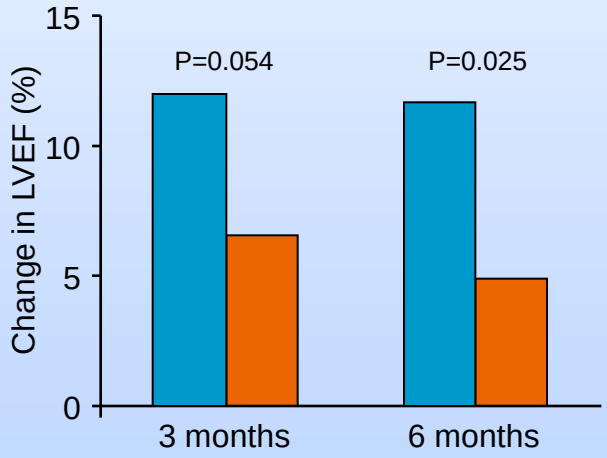
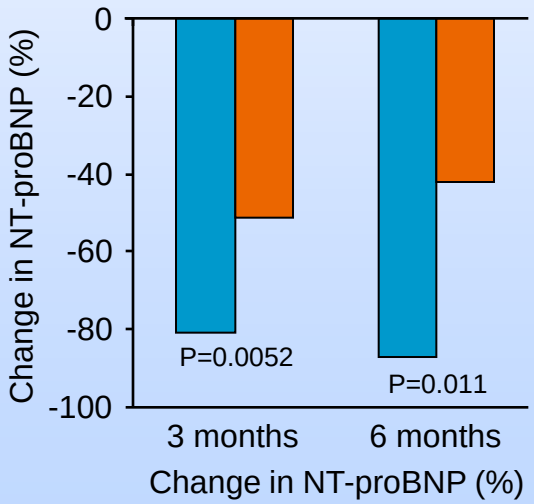
Heart Failure Medications







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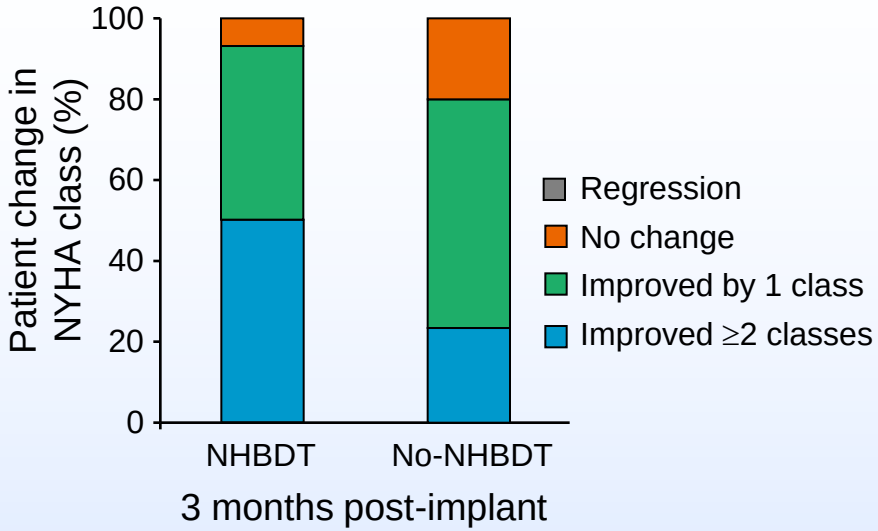
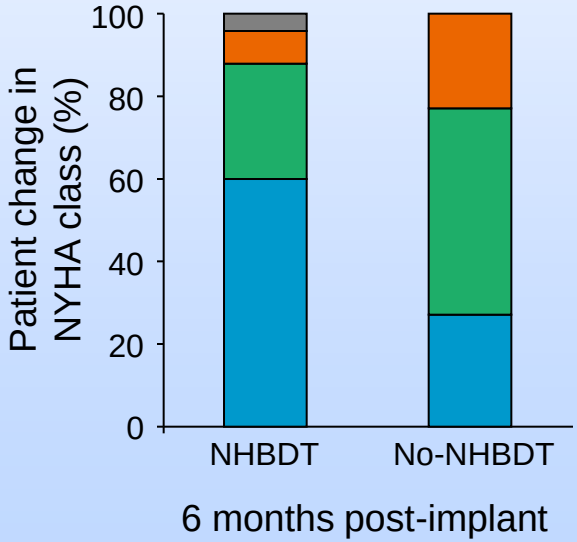
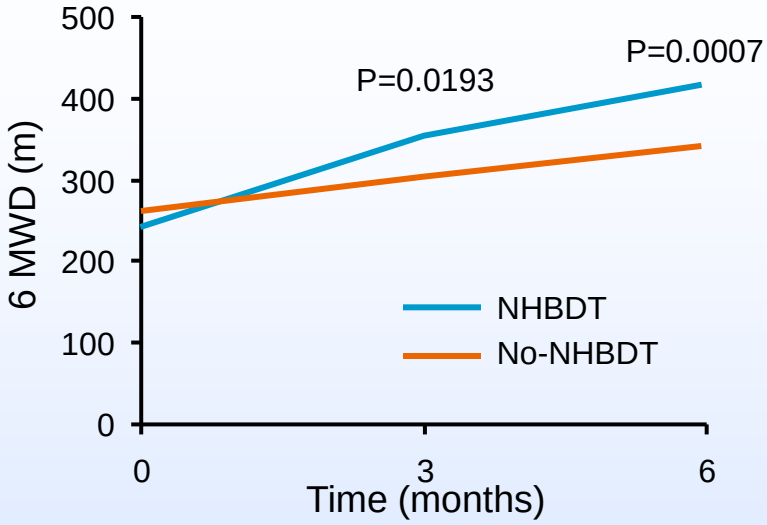
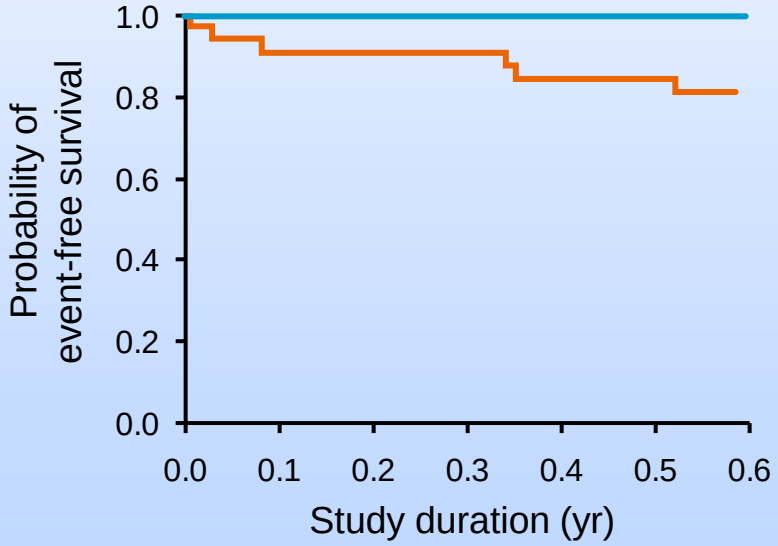








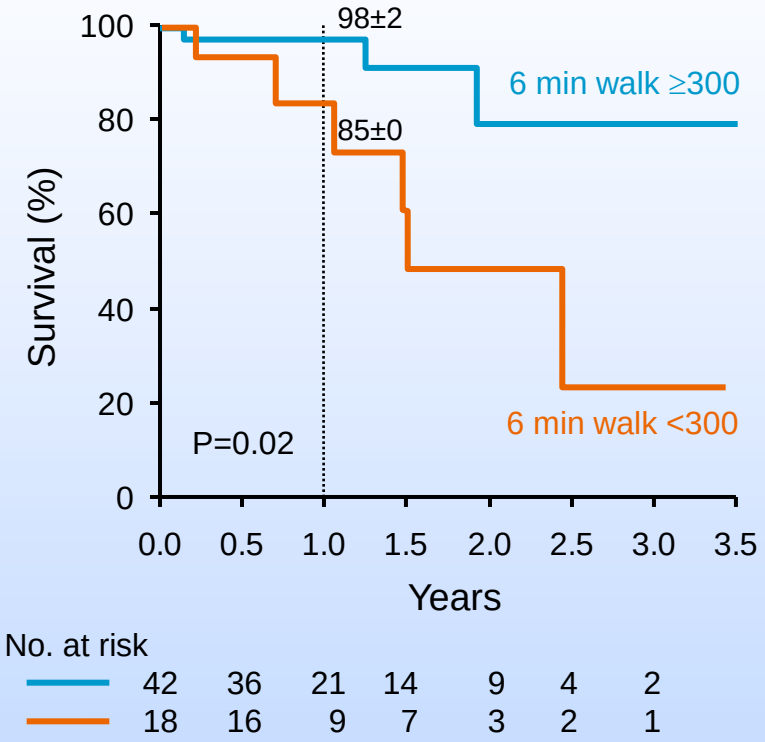
MAYO CLINIC

Rehabilitation

All
60
(6 MW available)
355±110 m
3.8 (3.0; 6.0) mo

Better performers
42/60 (70%)
6 MW ≥300 m
406m (343; 478)
4.1 (3.1; 6.1) mo

Poor performers
18/60 (30%)
6 MW <300 m
223m (198; 258)
3.4 (3.0; 6.0) mo



MAYO CLINIC

Neurology/Psychiatry

- “Pump head”
- Embolic stroke
- Intracerebral bleeding

MAYO CLINIC

“Pump Head”

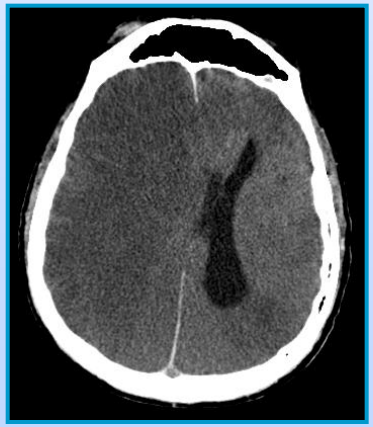
The role of cerebral hyperperfusion in postoperative neurologic dysfunction after left ventricular assist device implantation for end-stage heart failure

Katherine Lietz, MD, PhD,[a] Kevin Brown, DO,[f] Syed S. Ali, MD,[c] Monica Colvin-Adams, MD,[d] Andrew J. Boyle, MD,[d] David Anderson, MD,[f] Alan D. Weinberg, MS,[c] Leslie W. Miller, MD,[g] Soon Park, MD,[h] Ranjit John, MD,[e] and Ronald M. Lazar, PhD[b]

The Journal of Thoracic and Cardiovascular Surgery, April 2009

Rapid increase in cardiac output (flushing)

- Insomnia
- Altered mentation
- Hallucinations
- Psychosis
- Edema and herniation



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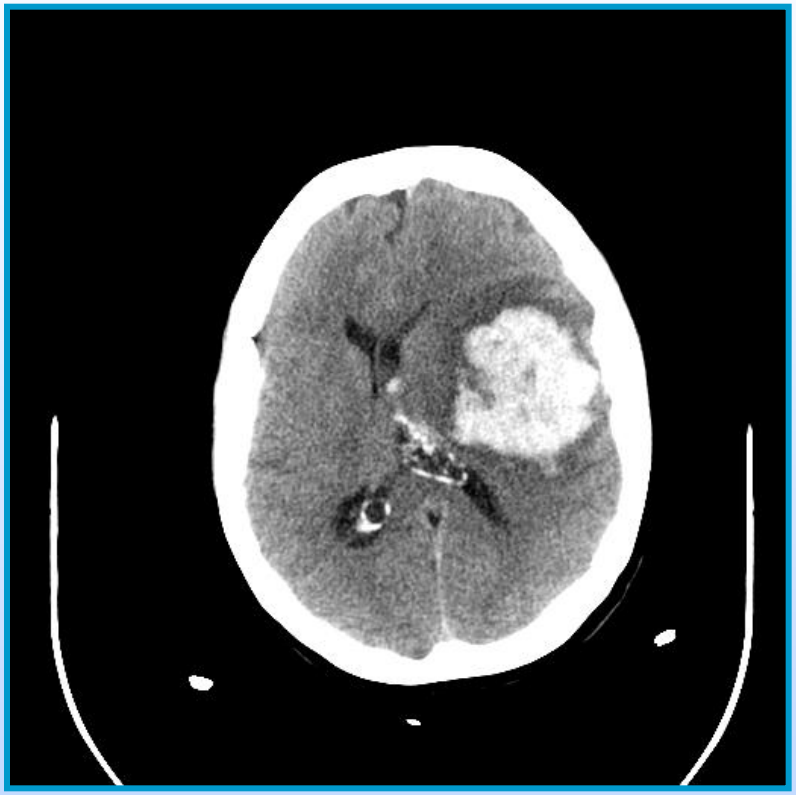
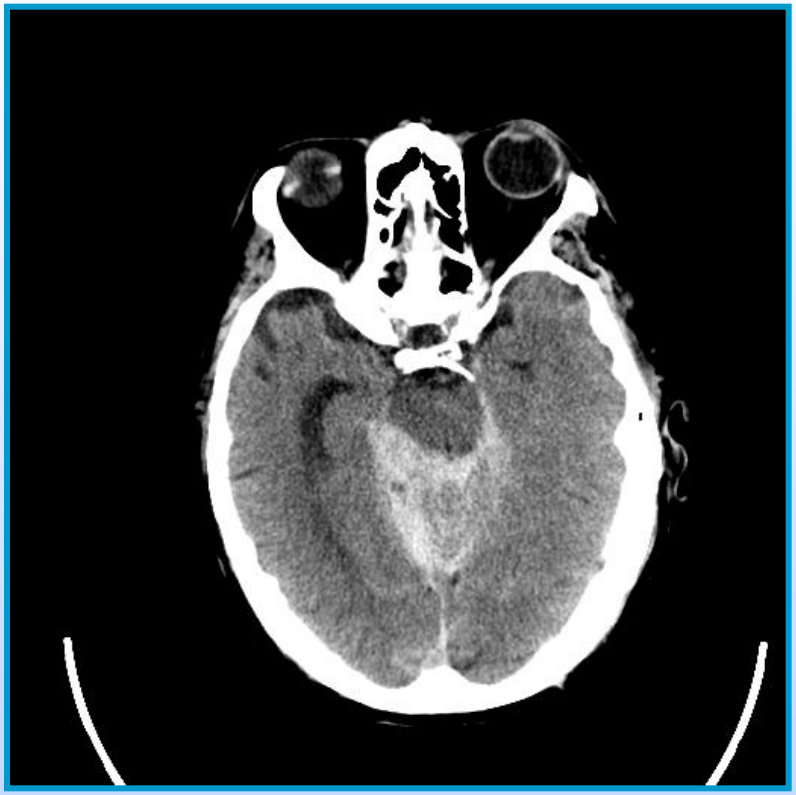
Bleeding





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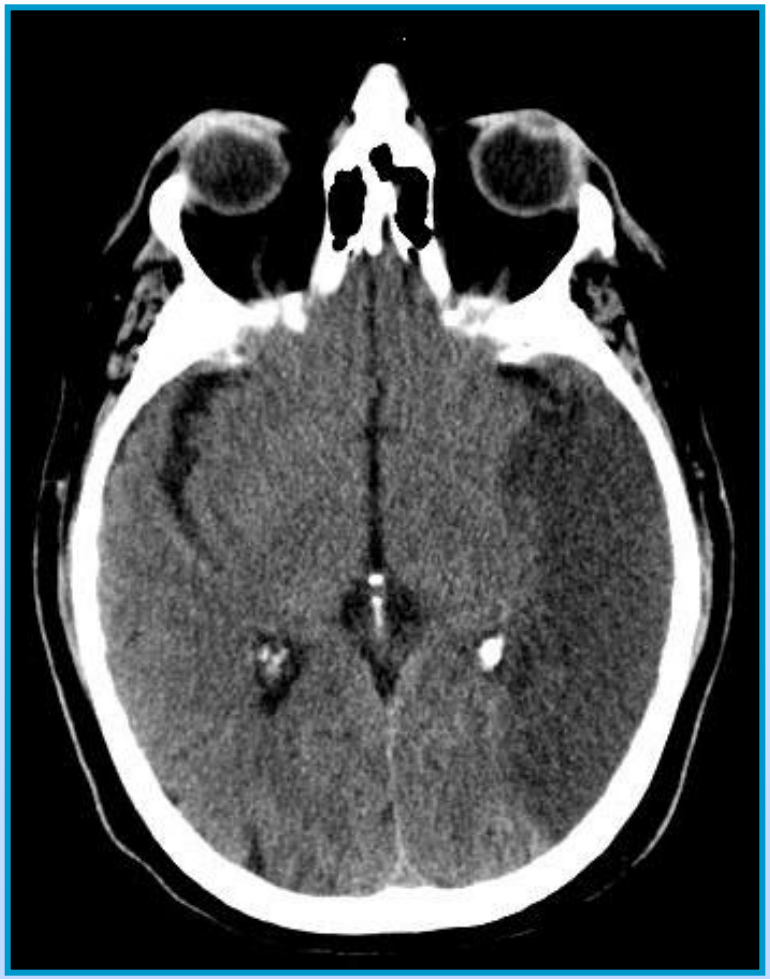
Stroke



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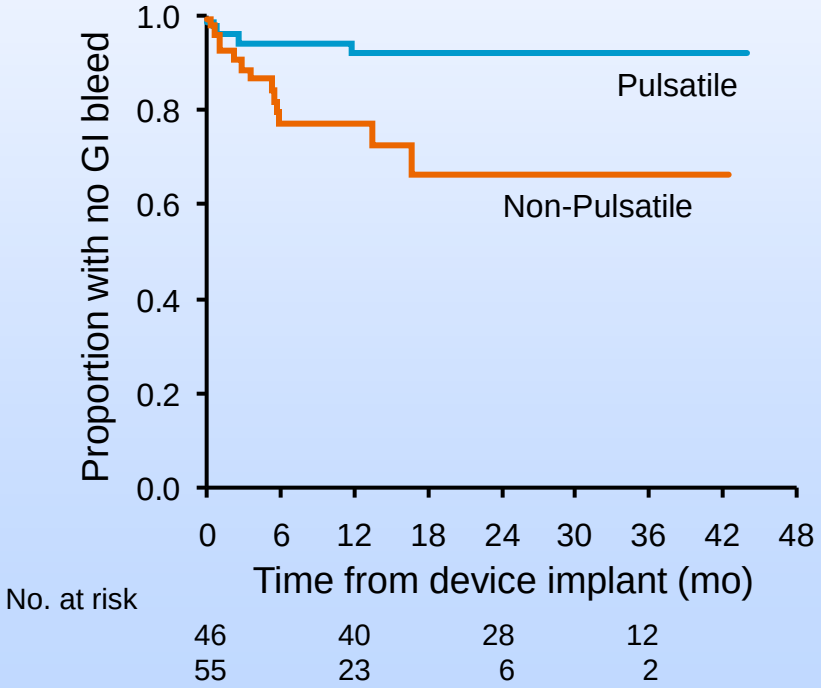
Gastroenterology
GI Bleeding

Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices

Sheri Crow, MD, MS,[a] Ranjit John, MD,[b] Andrew Boyle, MD,[c] Sara Shumway, MD,[b] Kenneth Liao, MD, PhD,[b] Monica Colvin-Adams, MD,[c] Carol Toninato, RN,[b] Emil Missov, MD,[c] Marc Pritzker, MD,[c] Cindy Martin, MD,[c] Daniel Garry, MD, PhD,[c] William Thomas, PhD,[d] and Lyle Joyce, MD, PhD[b]



The Journal of Thoracic and Cardiovascular Surgery , April 2009

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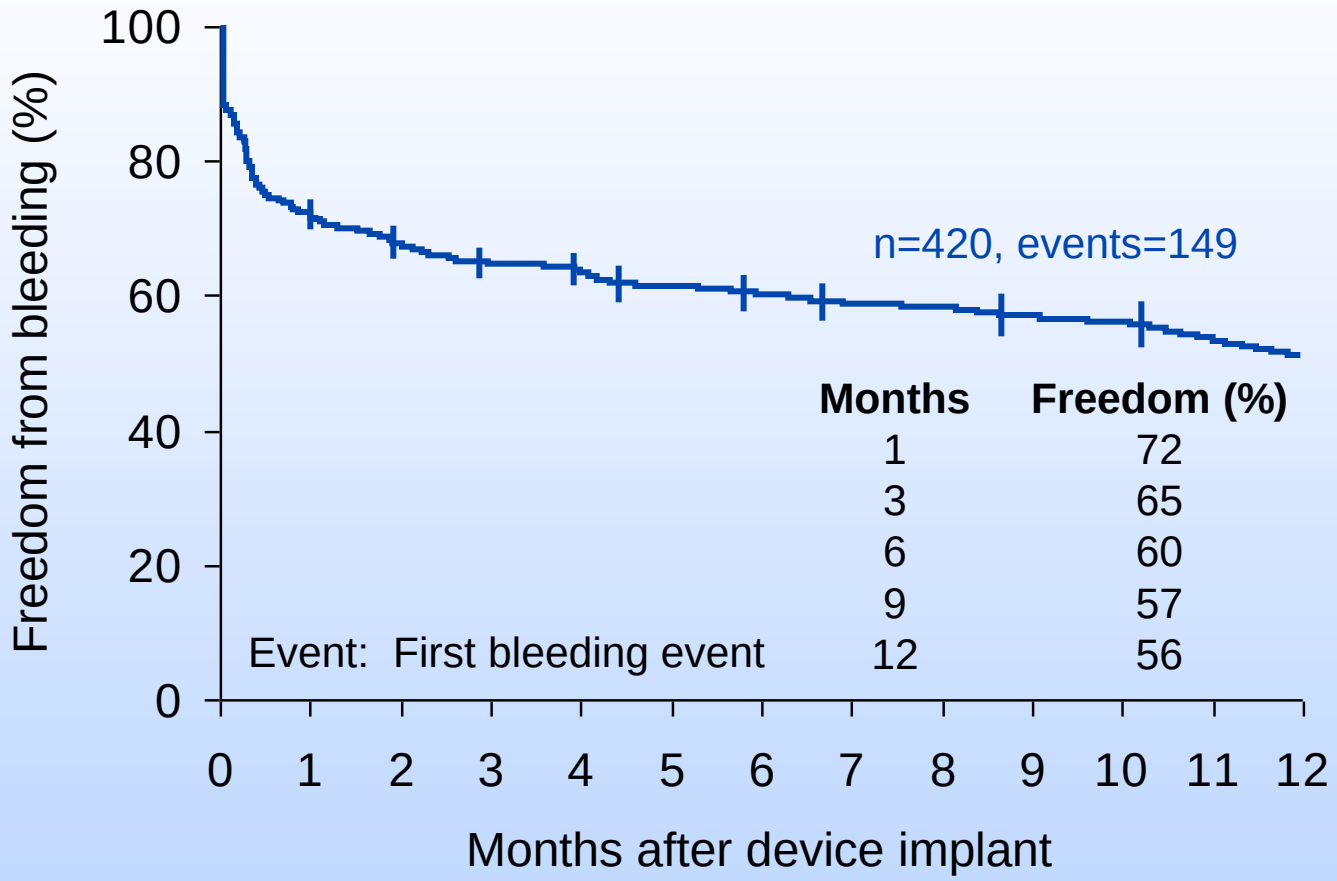
INTERMACS

INTERMACS: June 2006 – December 2007 Time to 1st Bleeding



J Heart Lung Transplant 27:1065, 2008

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GI Bleeding

- Stopping anticoagulation

Discontinuation of antithrombotic therapy for a year or more in patients with continuous-flow left ventricular assist devices☆

Naveen L. Pereira[a,*], Dong Chen[b], Sudhir S. Kushwaha[a], Soon J. Park[c]

Interactive CardioVascular and Thoracic Surgery 11 (2010) 503-506

- Endoscopy (upper, lower), double baloon, capsule.
- Pathology (AVM)
- Treatment: local, anti-acid (?Danazol, ?Octreotide)

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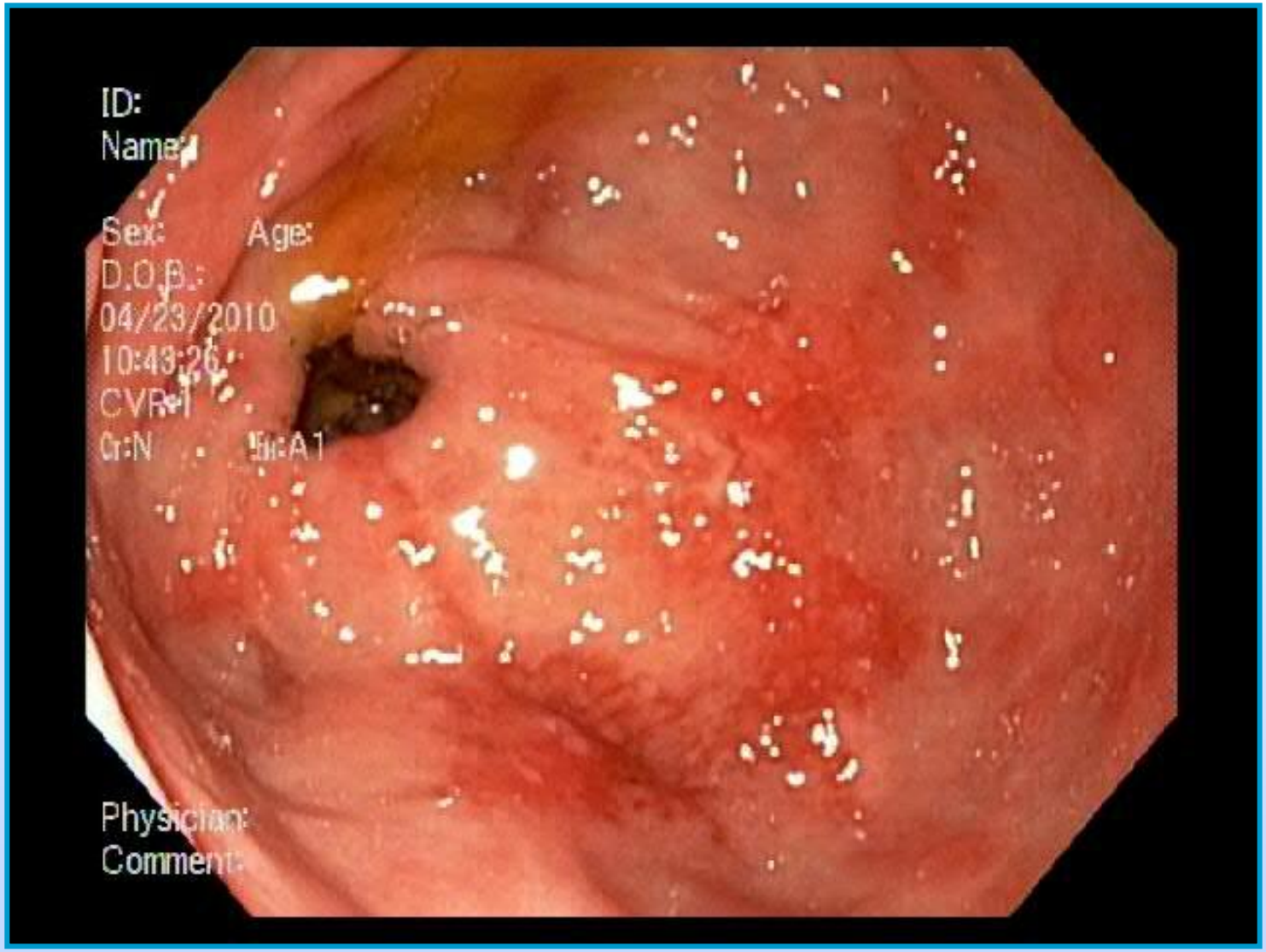
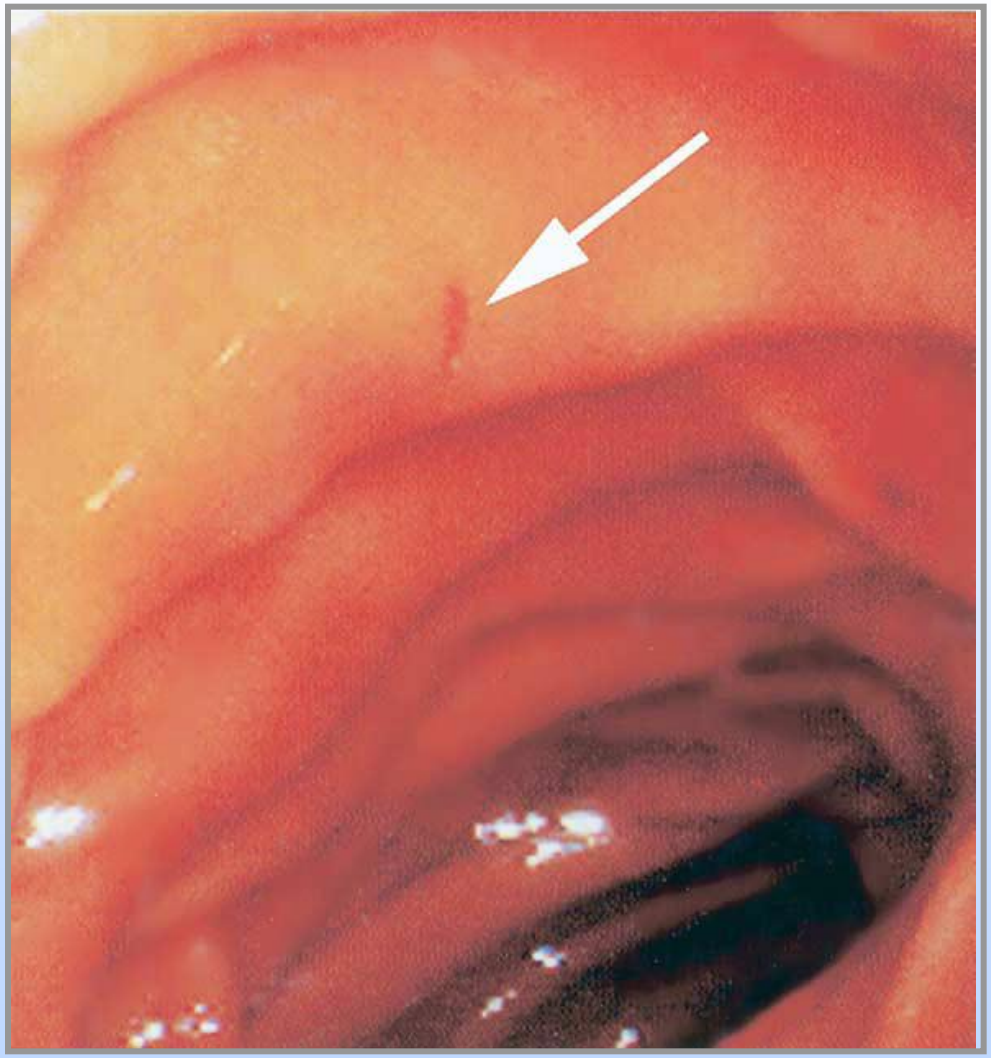


Ileal AVM with Bleeding



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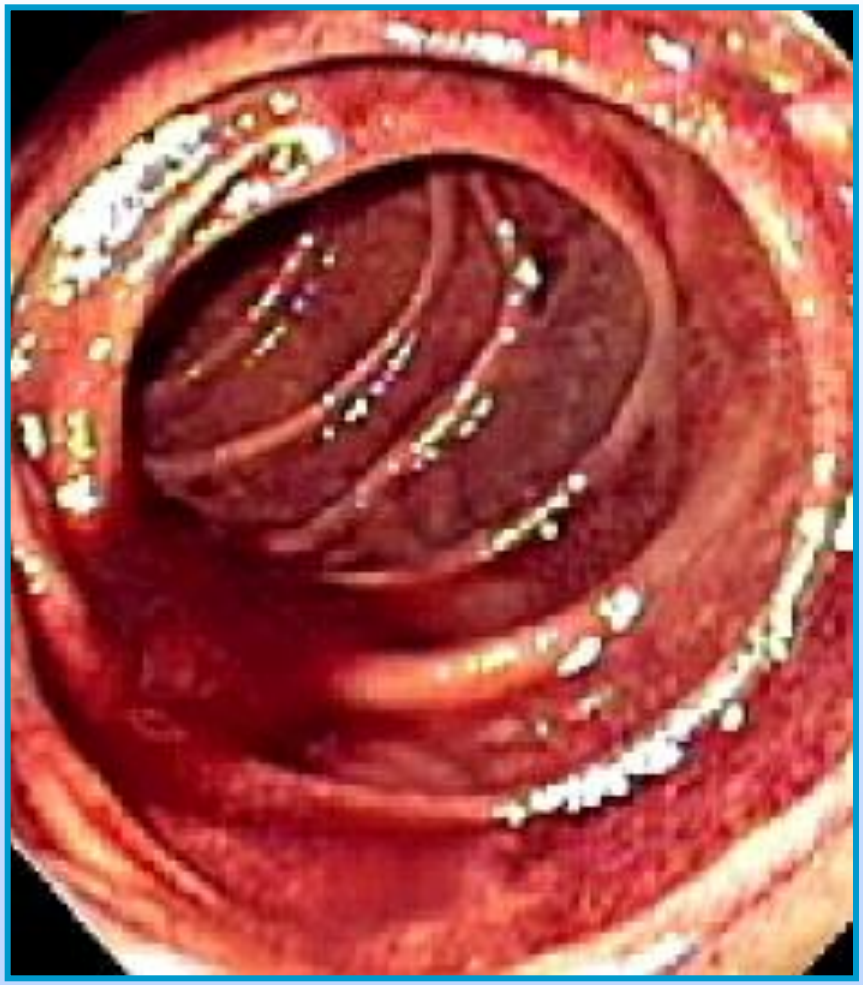
Actively Bleeding AVM
Duodenum



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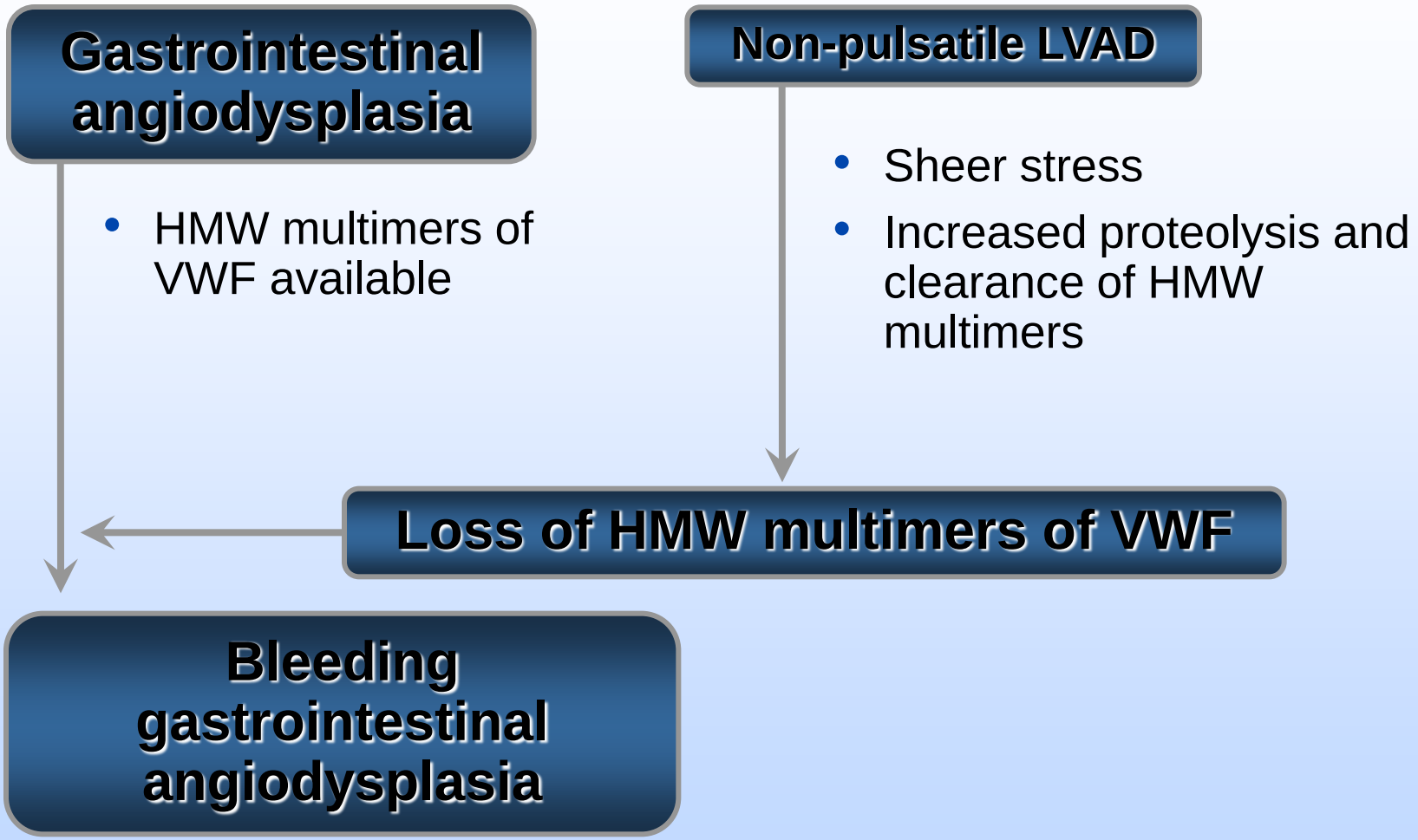
Non-pulsatile LVAD and GI Bleeding



Warkentin et al: Transfusion Medicine Reviews 17: 272, 2003

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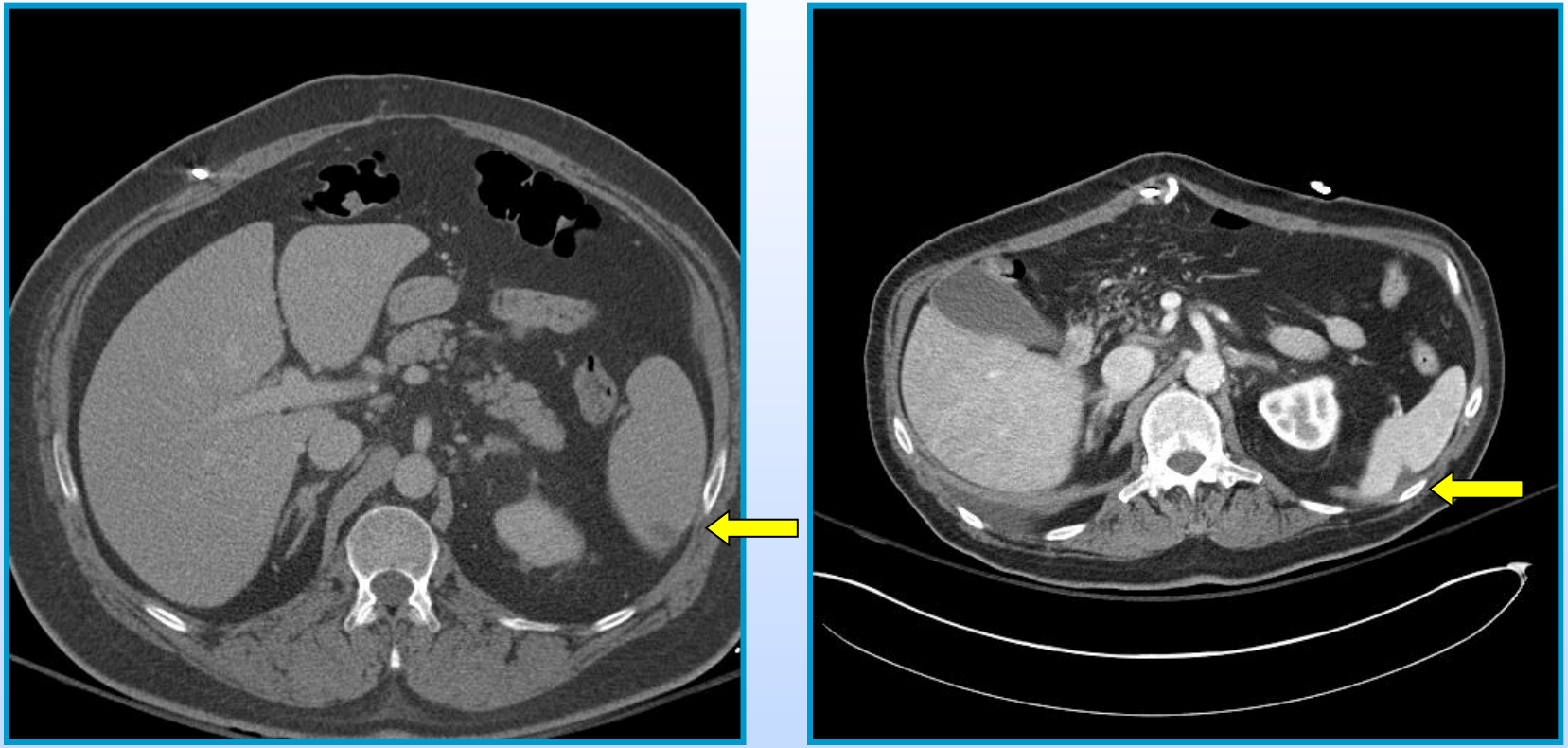
Infarcts (Splenic)



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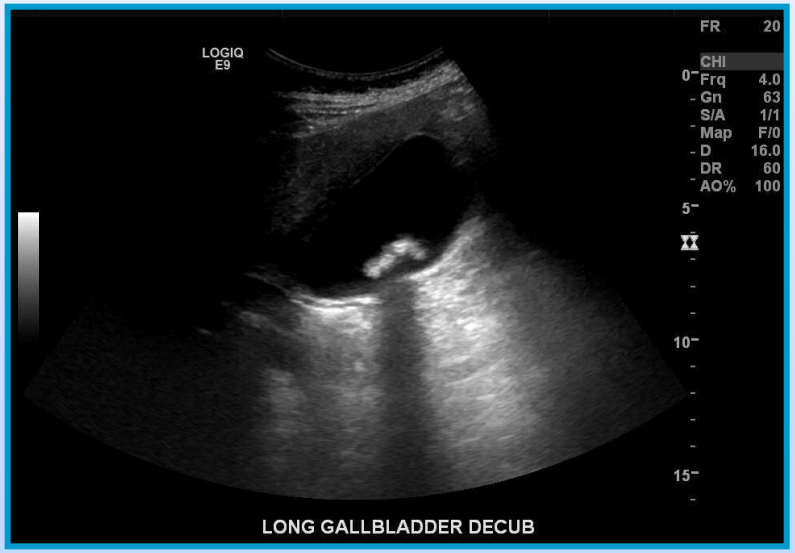
Hepatology

- Bile stones (pigment?)
- Bile duct malignancy
- Post-operative hyperbilirubinemia



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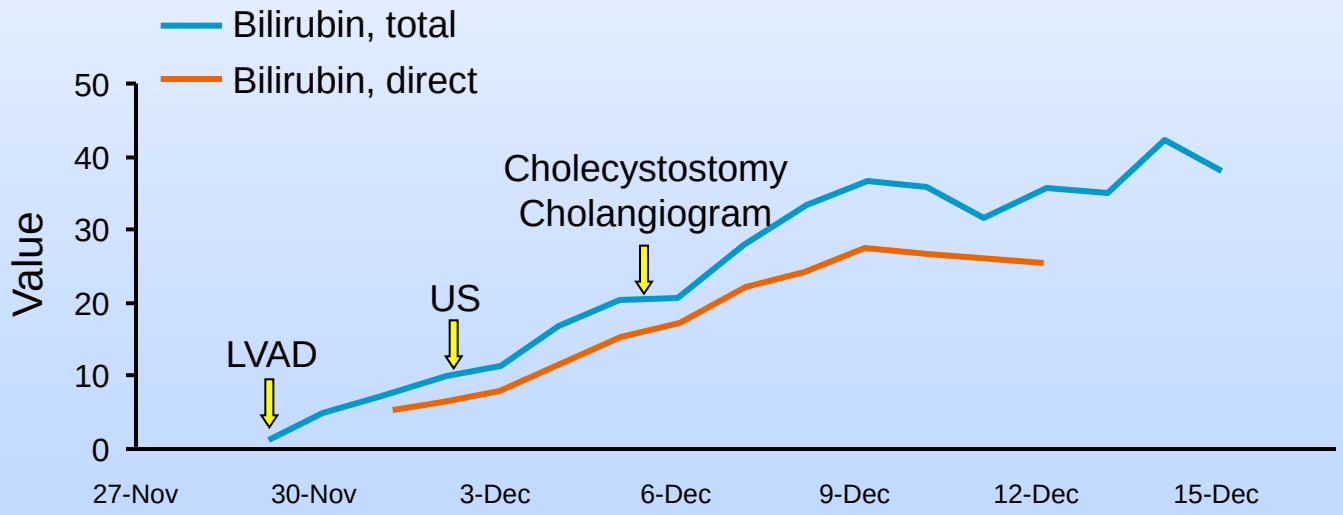
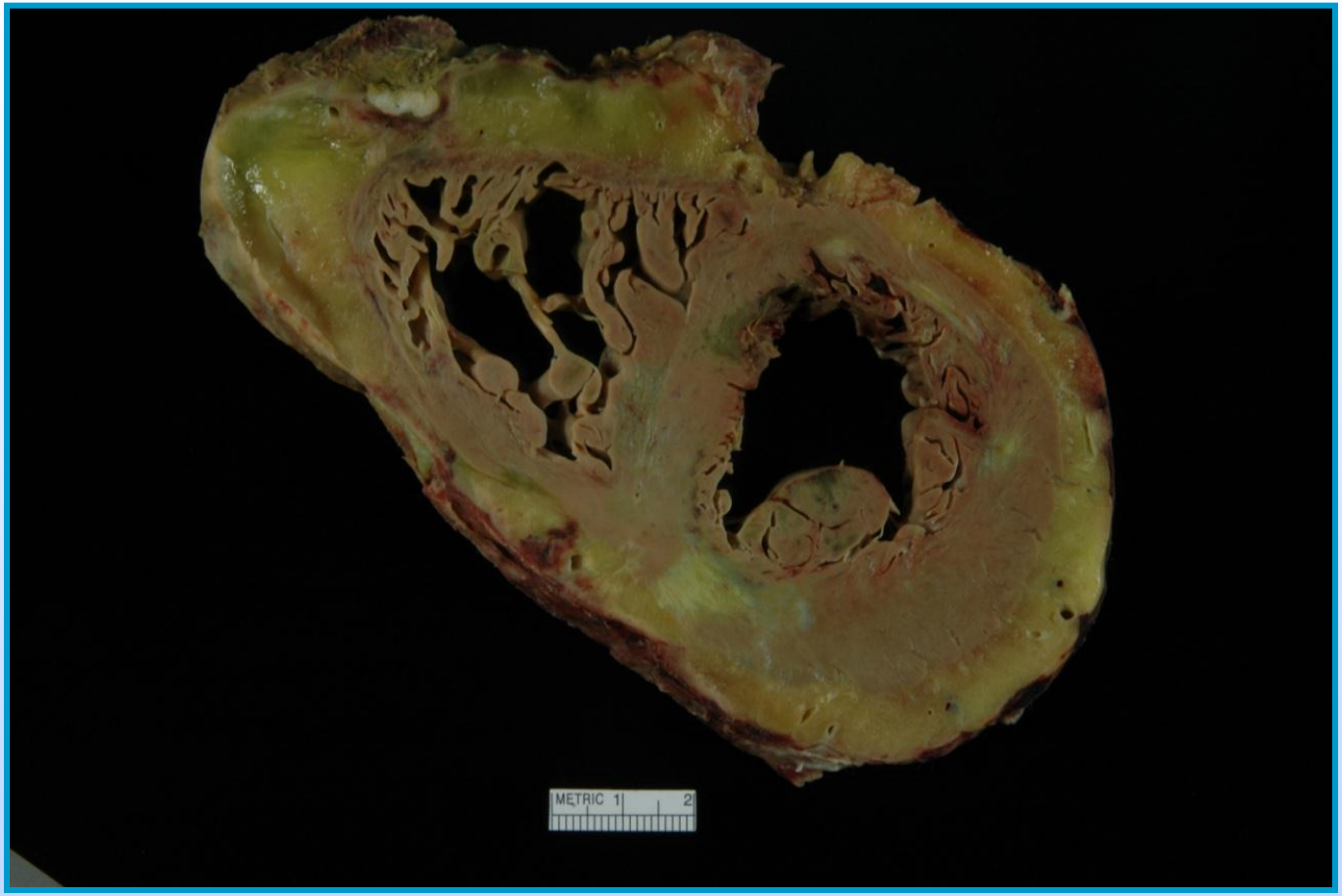
Post-Operative Hyperbilirubinemia

- 73, Ischemic CM, 4 years on Milrinone
- Hx of cholelithiasis
- Postoperative encephalopathy



MAYO CLINIC

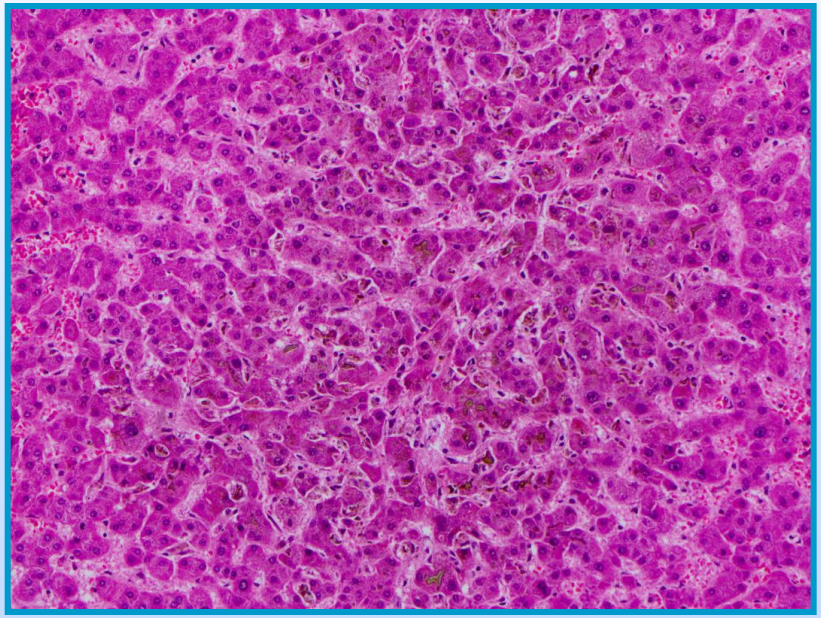
Post-Operative Hyperbilirubinemia



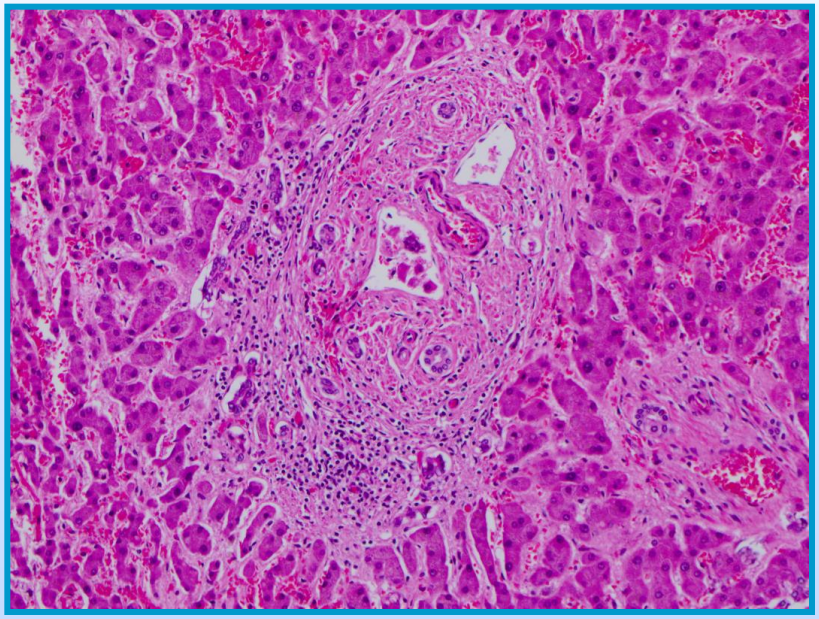
MAYO CLINIC

Post-Operative Hyperbilirubinemia

Canalicular and Intracellular Cholestasis



Bile Duct Proliferation and Fibrosis

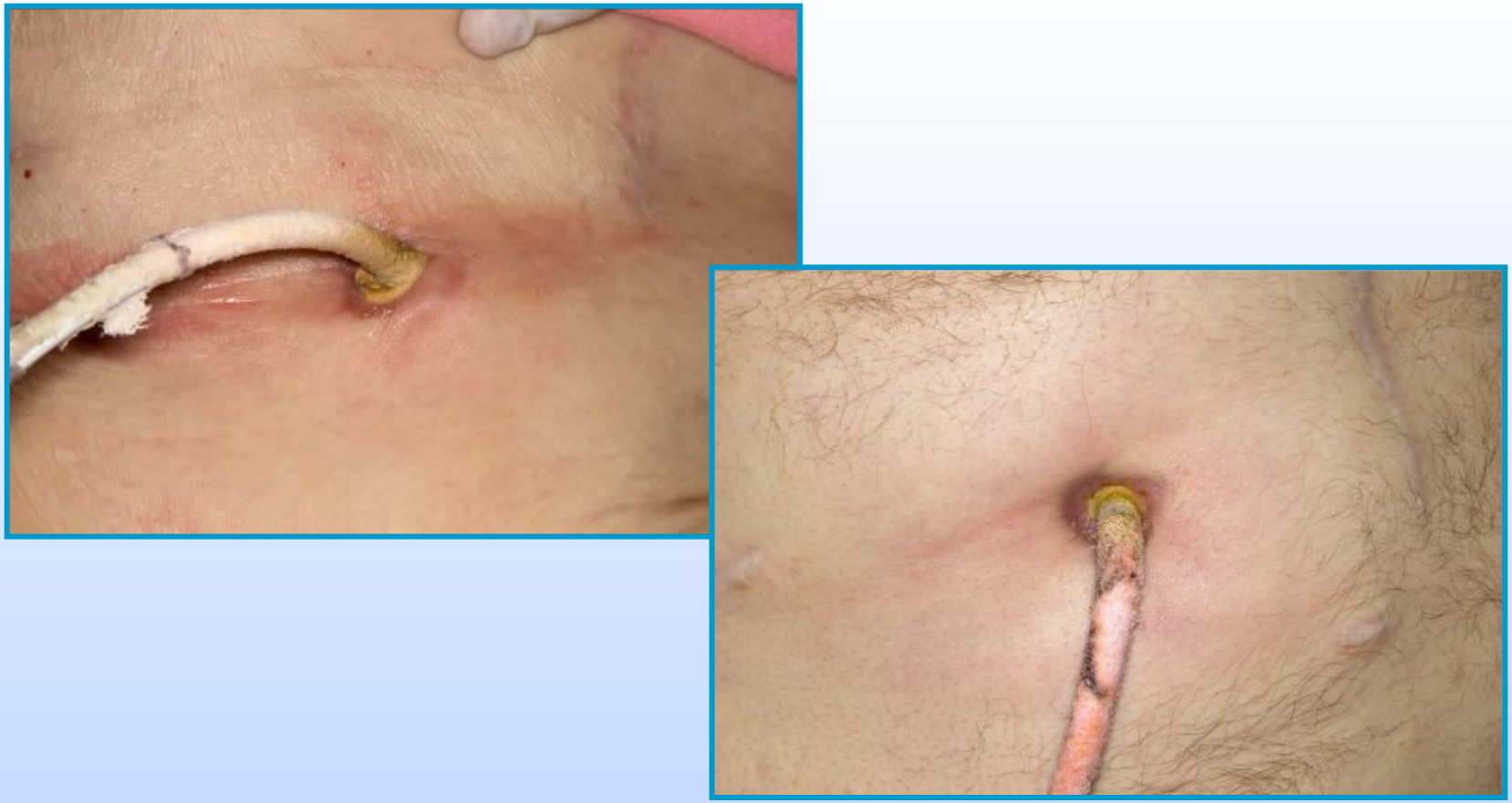


MAYO CLINIC

Infectious Disease

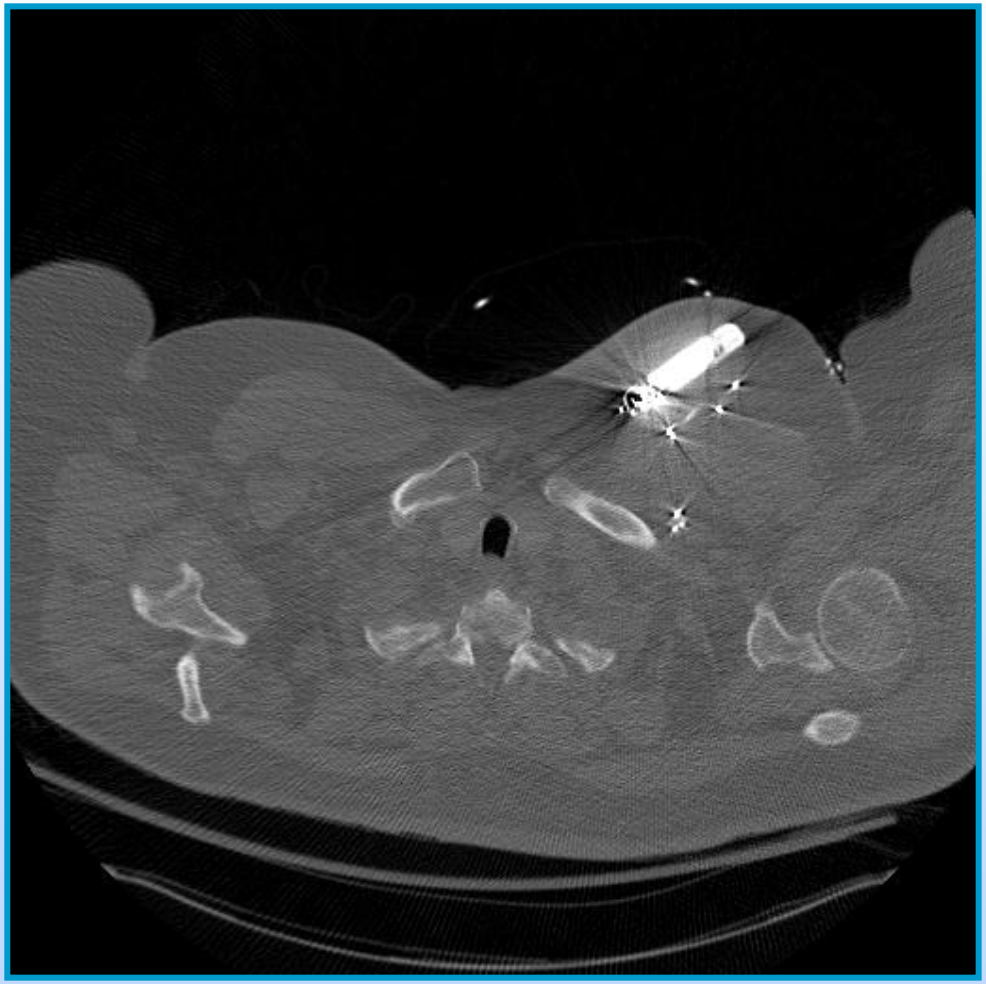
- Driveline infections: Stulak et al
- Total incidence of infectious events per patient-years of support
  - 0.12 University of Michigan (proph Abx)
  - 0.036 Mayo (no proph Abx) (P=0.26)

MAYO CLINIC



MAYO CLINIC

Infectious Disease – Device Infections



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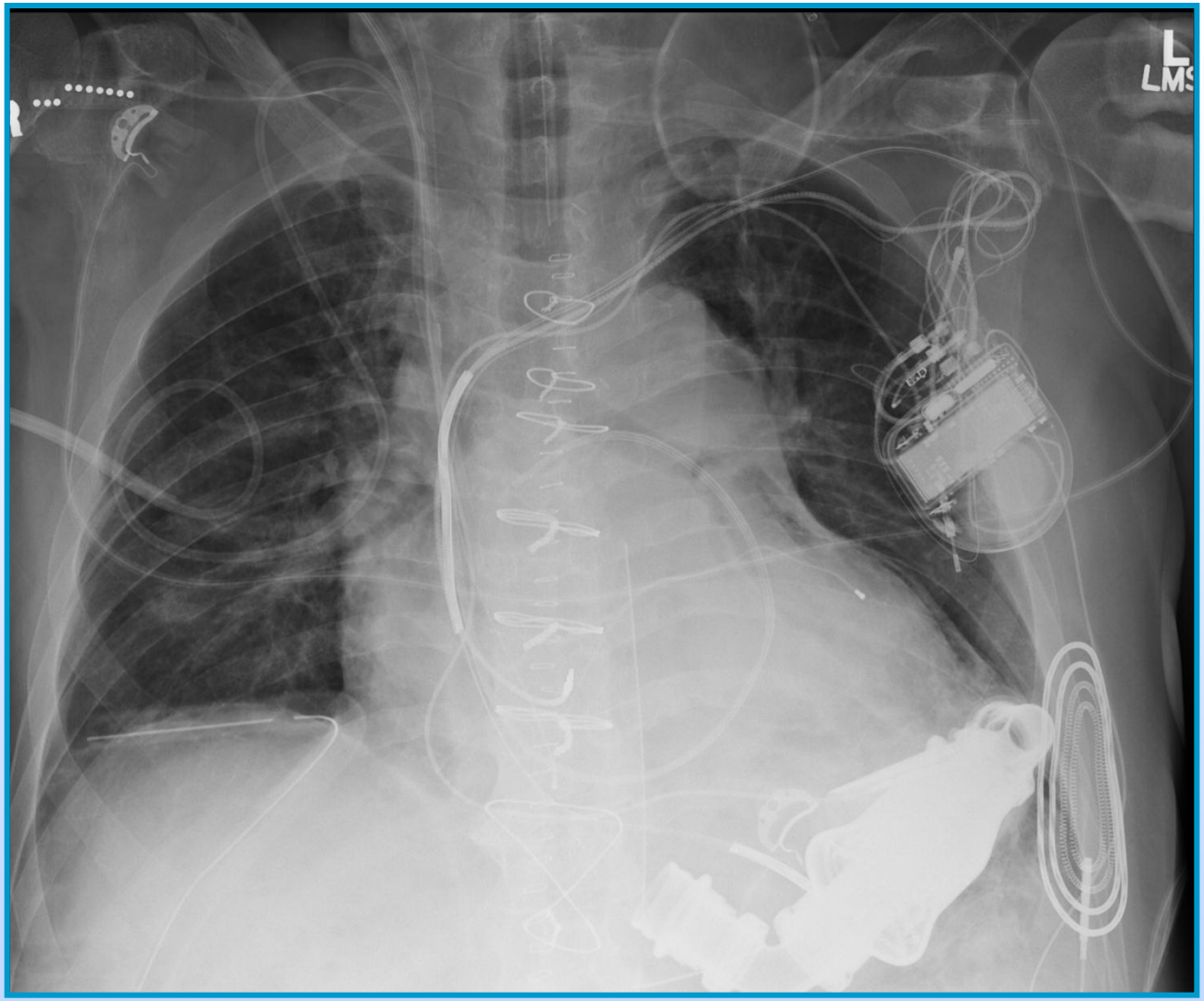
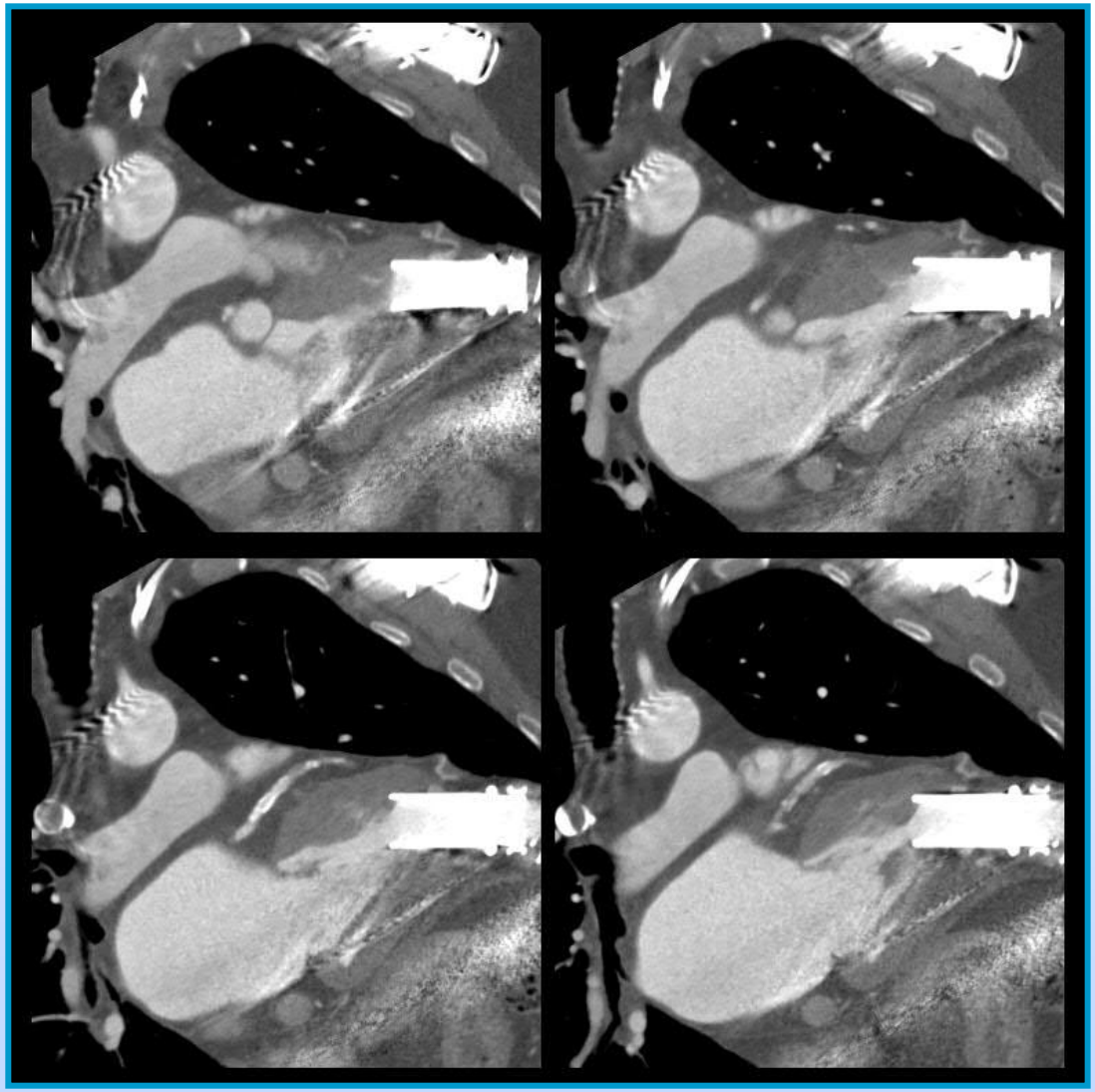


MAYO CLINIC



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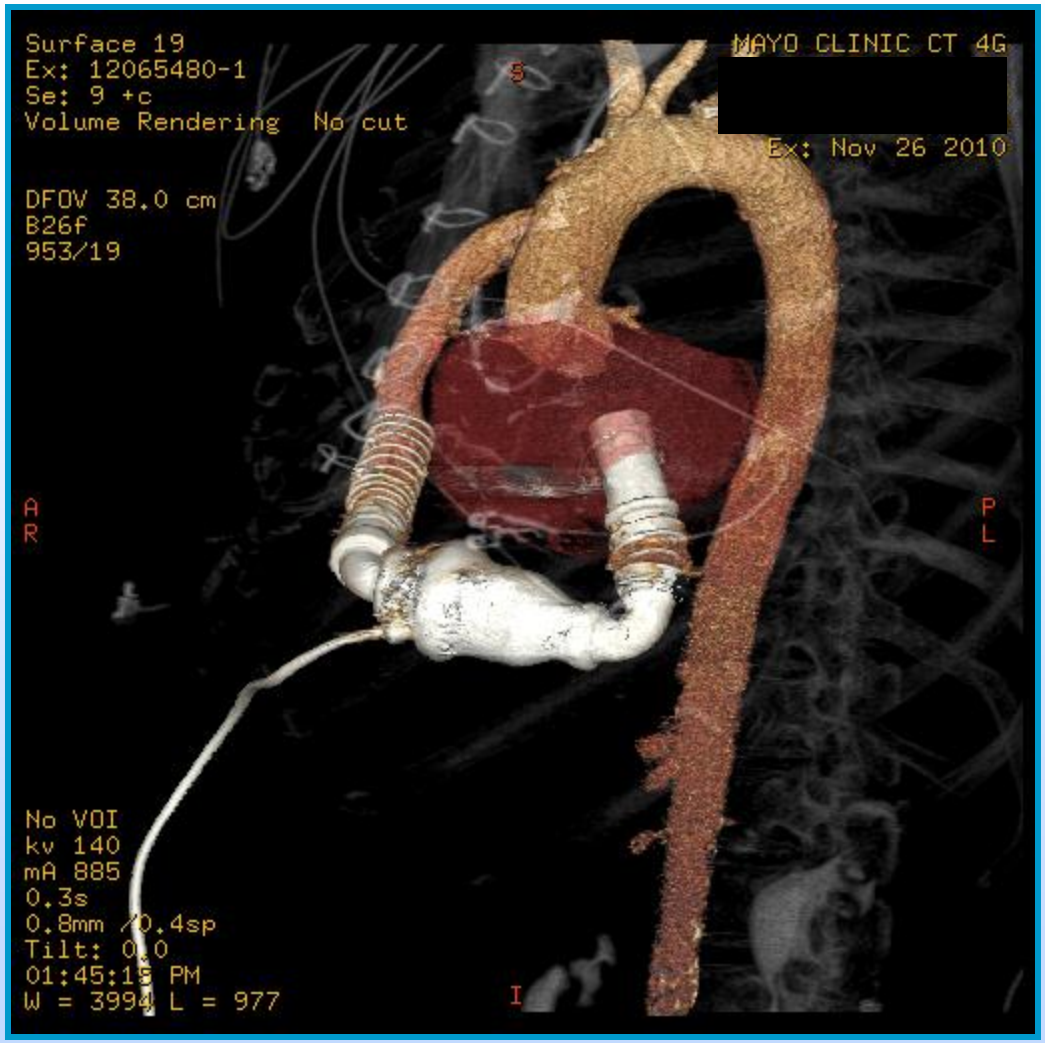

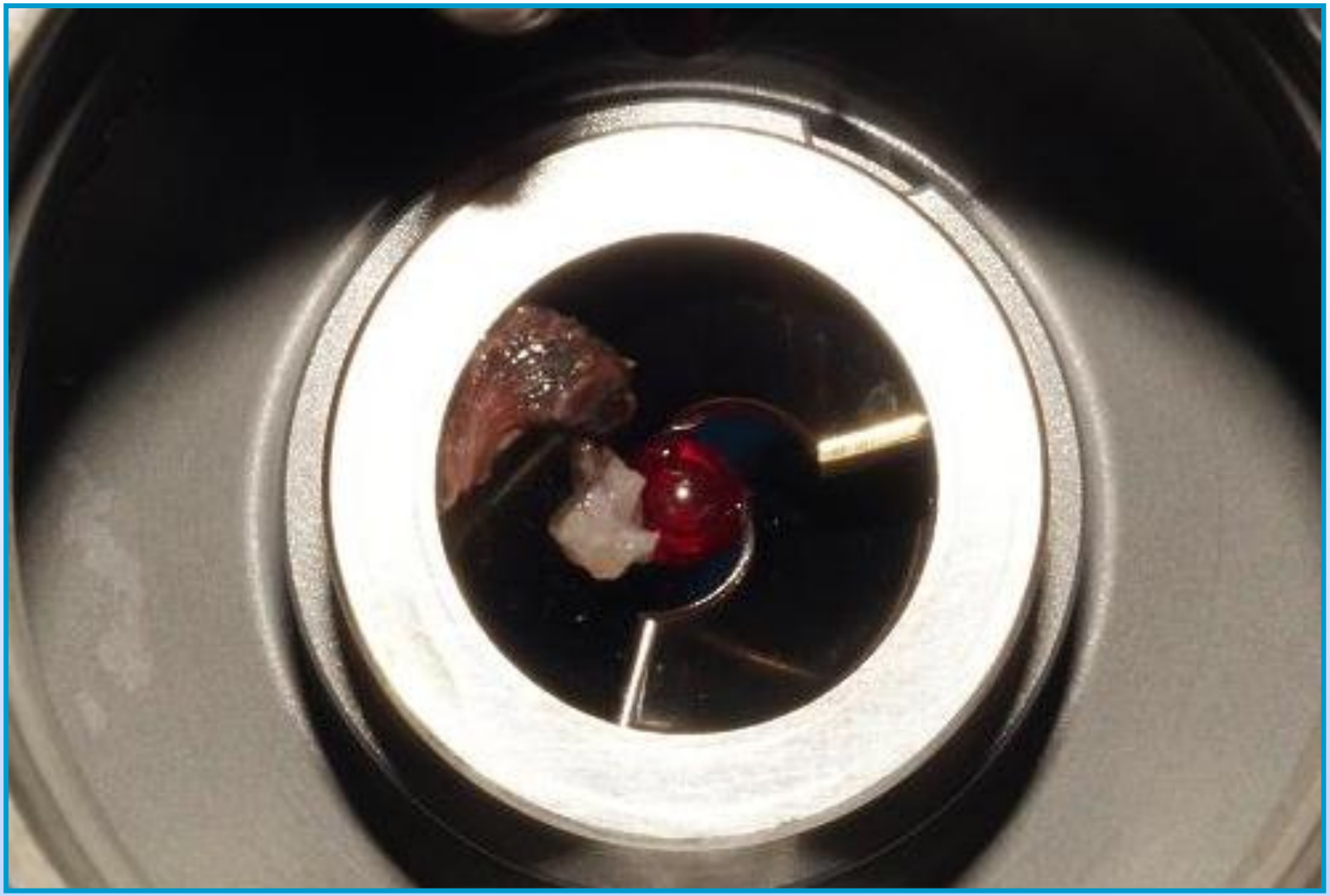

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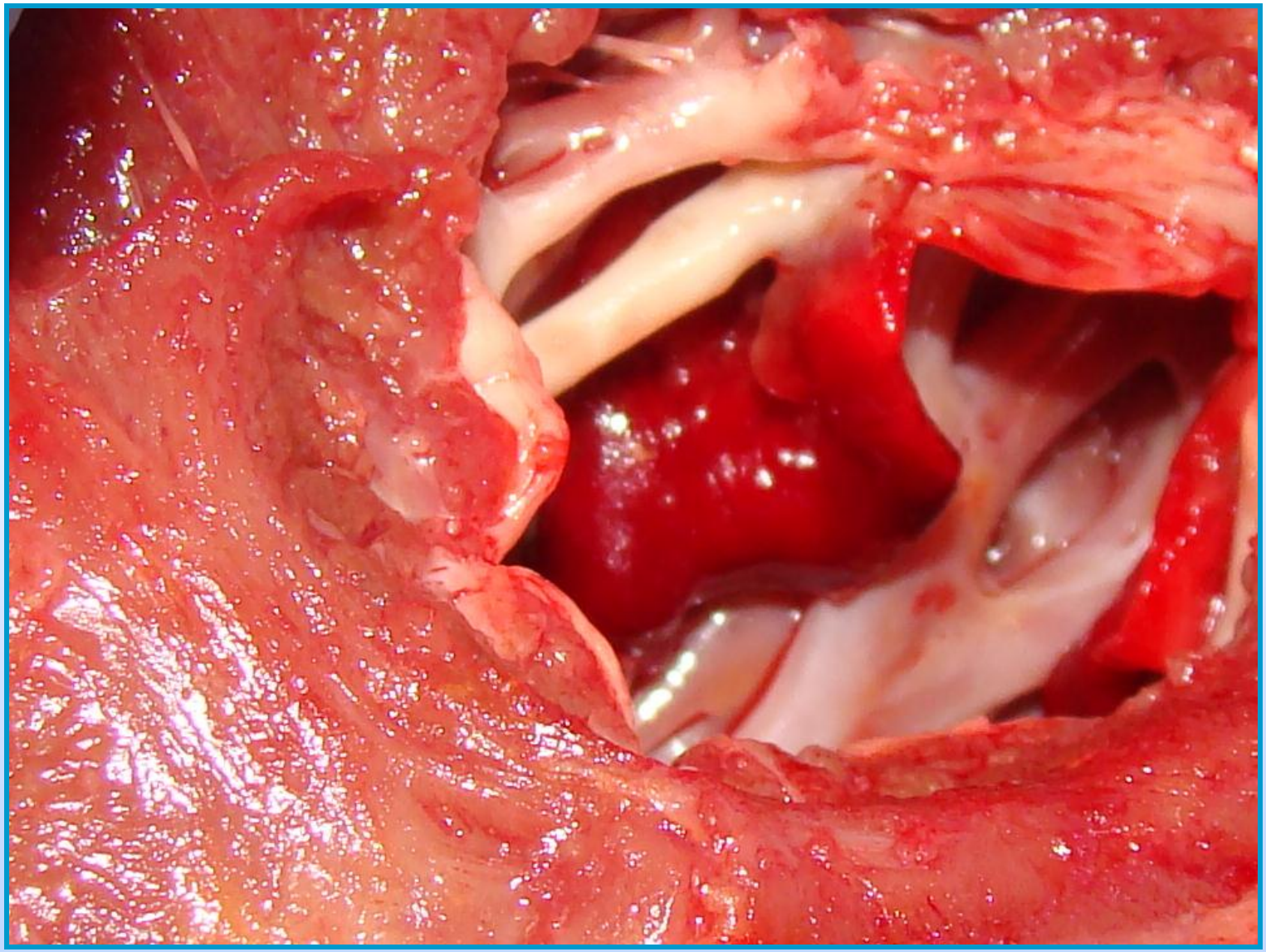

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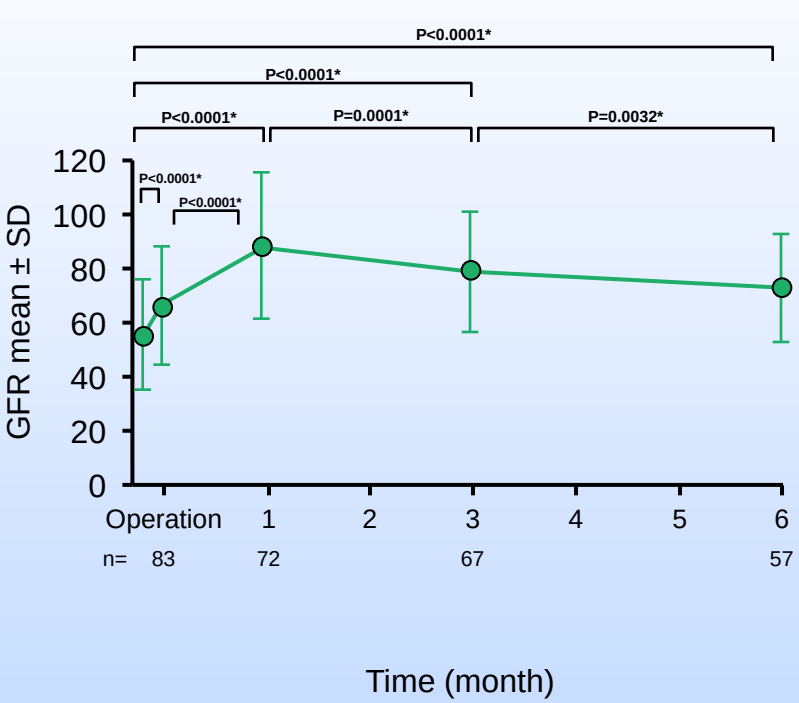
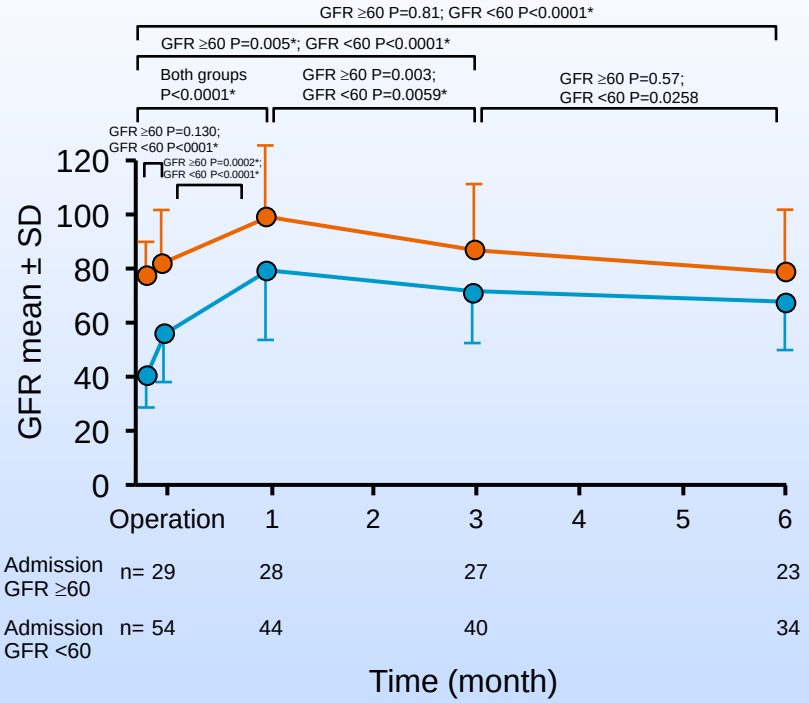
Nephrology

GFR change after LVAD with time all patients



GFR change after LVAD with time by subgroups



10% ARF after LVAD necessitating hemodialysis; 2 died early post-operative, 2 recovered; 5% chronic hemodialysis

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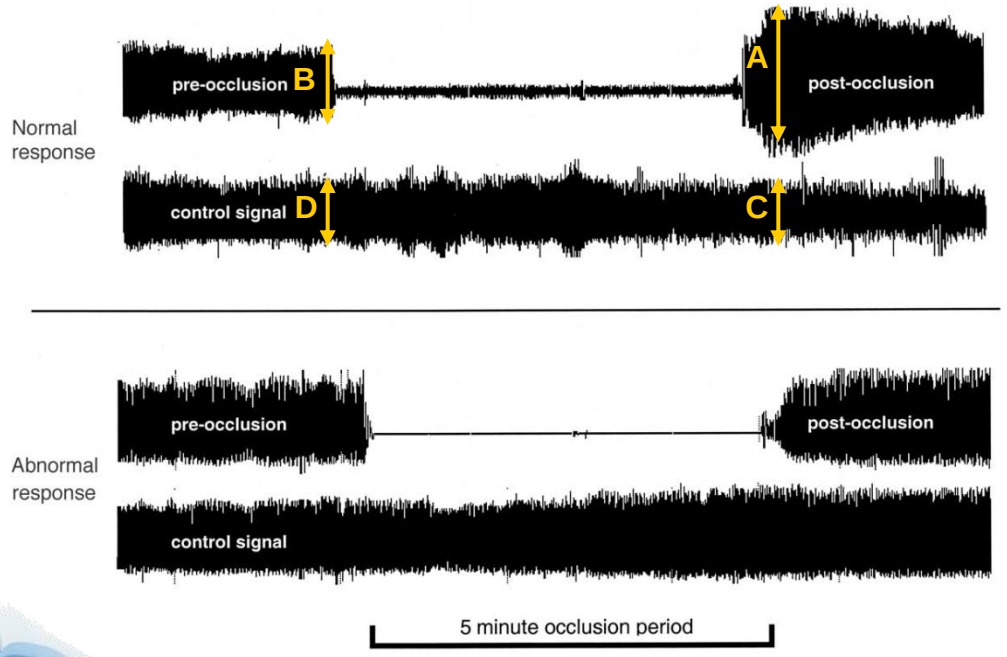
Vascular Medicine
Endothelial Function



$$RHI = \frac{A/B}{C/D}$$ normal >1.67

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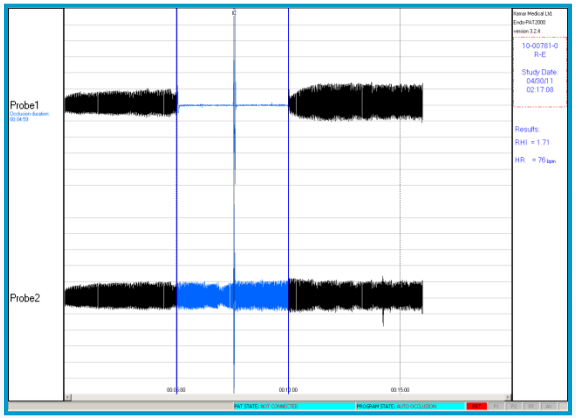
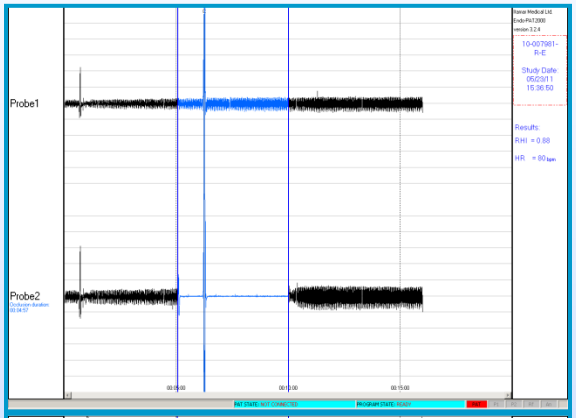


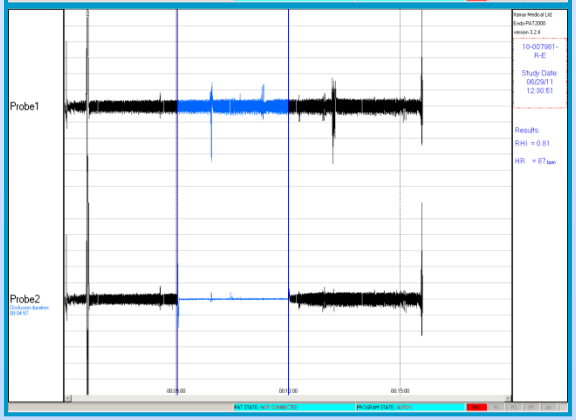
Pre-op

RHI=1.71



Early post-op

RHI=0.88



2 month

RHI=0.81

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Conclusions

- LVAD implantation offers improved morbidity and mortality to stage D HF patients
- A multidisciplinary team approach is crucial for the success of an LVAD program
- The new physiology during continuous flow support raises novel clinical questions calling for further research

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Thank You!

Hematologic Adverse Events

Summary of Reported Hematologic-Related Adverse Events from the Large Multicenter Clinical Trials with Continuous Flow LVADs

LVAD	Bleeding requiring surgery	Ischemic CVA	Hemorrhagic CVA	Pump thrombosis	Hemolysis
HeartMate II BTT US (281)	72 (0.45)	15 (0.09)	9 (0.05)	4 (0.02)	11 (0.06)
HeartMate II DT US (133)	40 (0.23)	11 (0.06)	15 (0.07)	5 (0.02)	5 (0.02)
HeartMate II Europe (101)	51 (1.14)	4 (0.09)	3 (0.05)	1 (0.02)	6 (0.13)
Duraheart (33)	4 (0.22)	1 (0.06)[a]	3 (0.17)[a]	0	0

Data are the number of patients with the event and in parenthesis is the event rate (events per patient-year)

BTT bridge to transplant, DT destination therapy, CVA cerebrovascular accident

[a] Total of 5 CVA, 1 event not listed as ischemic or hemorrhagic

J of Cardiovsc Trans Res 3:618, 2010

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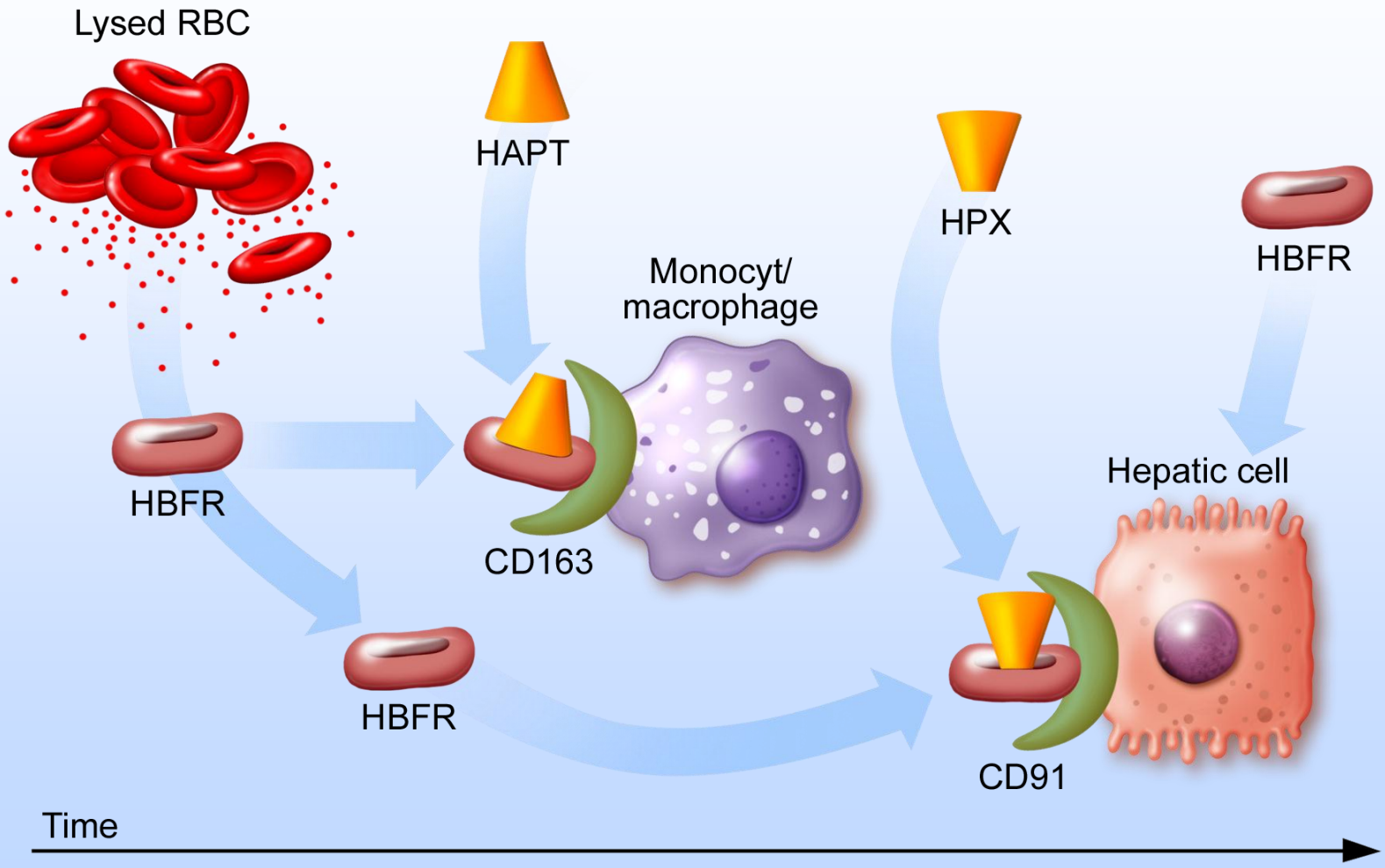
Gradual Removal of Free Hb



Heilmann 2009

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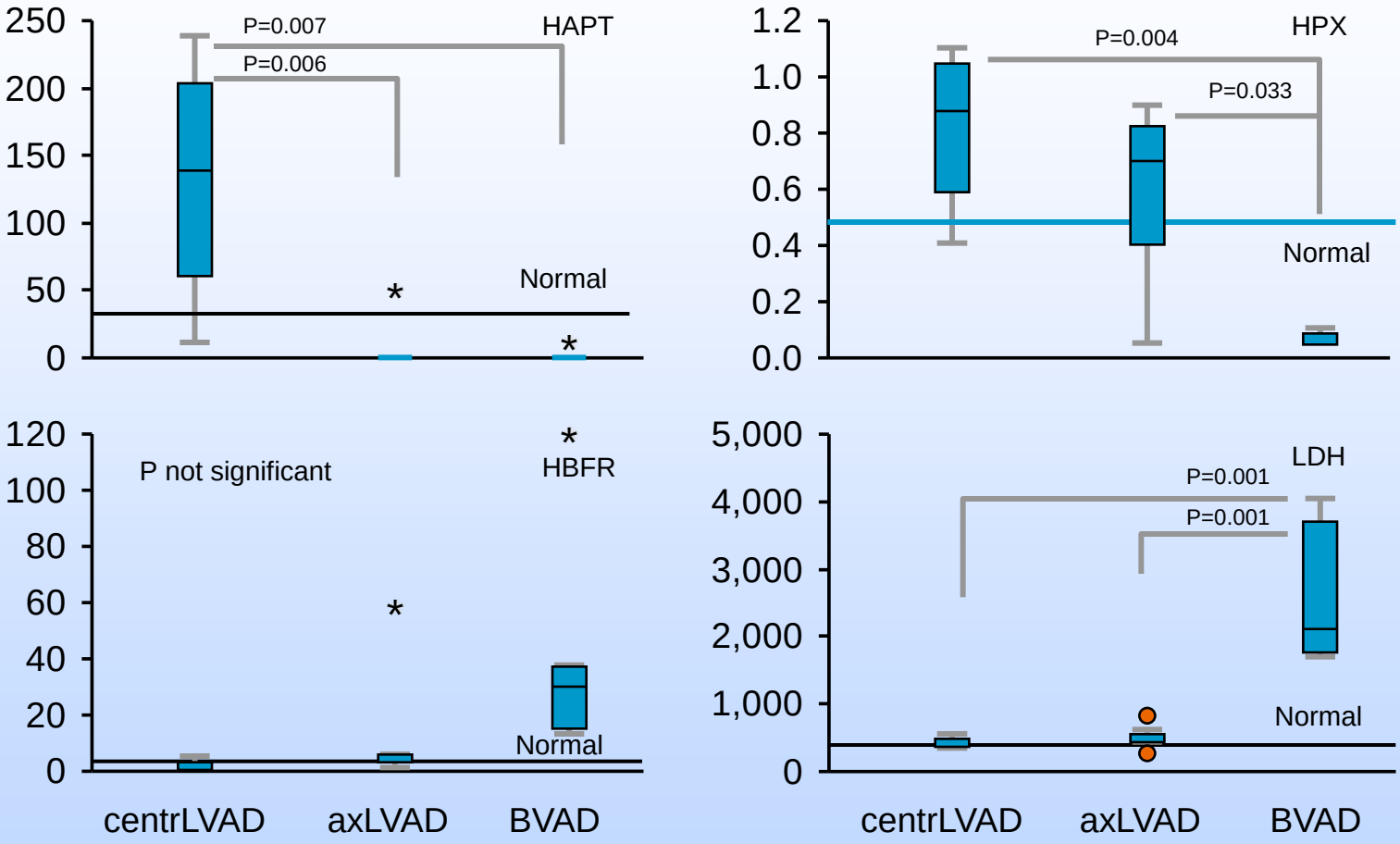
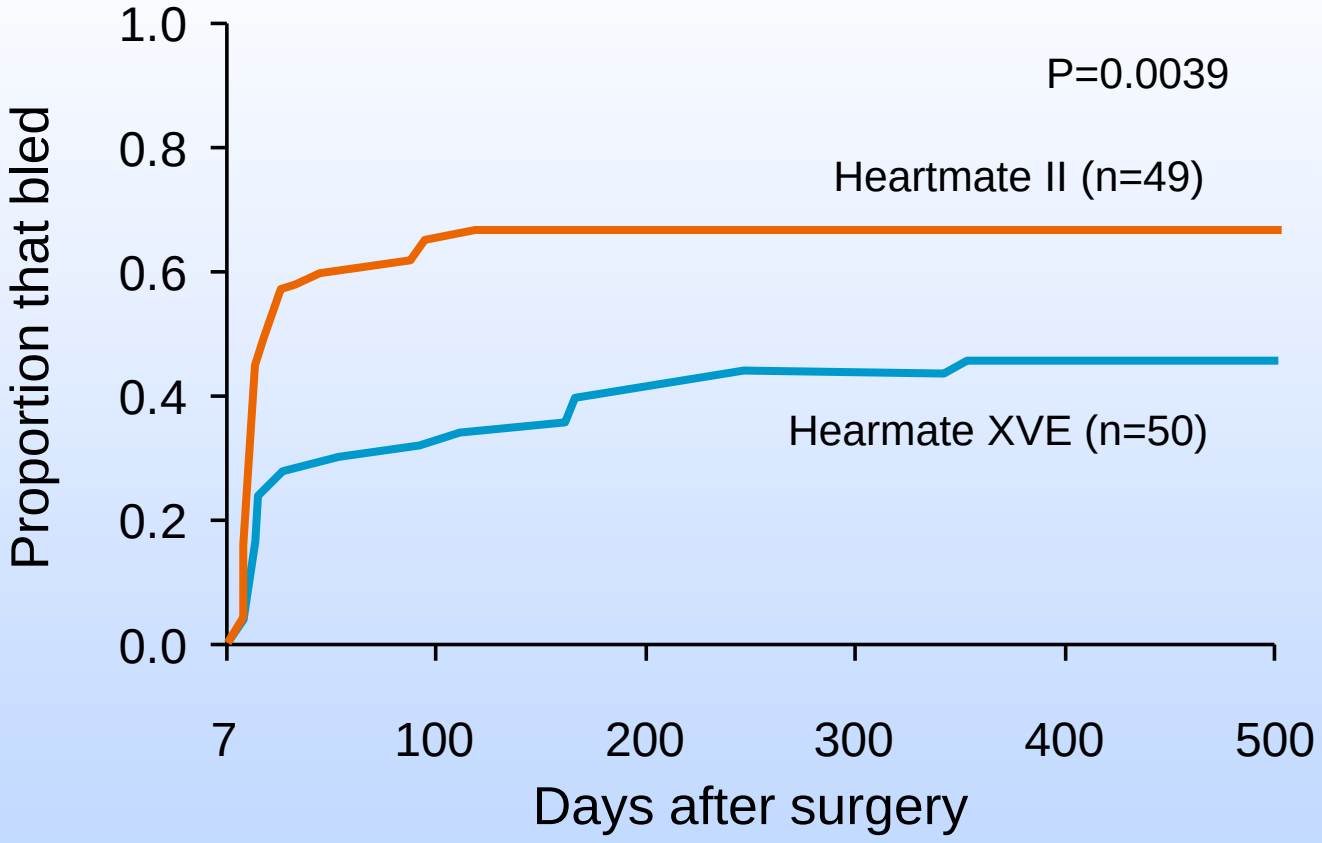
Comparison of VAD types and Hemolysis



Heilmann 2009

Post-LVAD Bleeding Events



Pedrotty et al: ISHLT 29th Annual Meeting, Paris, 2009

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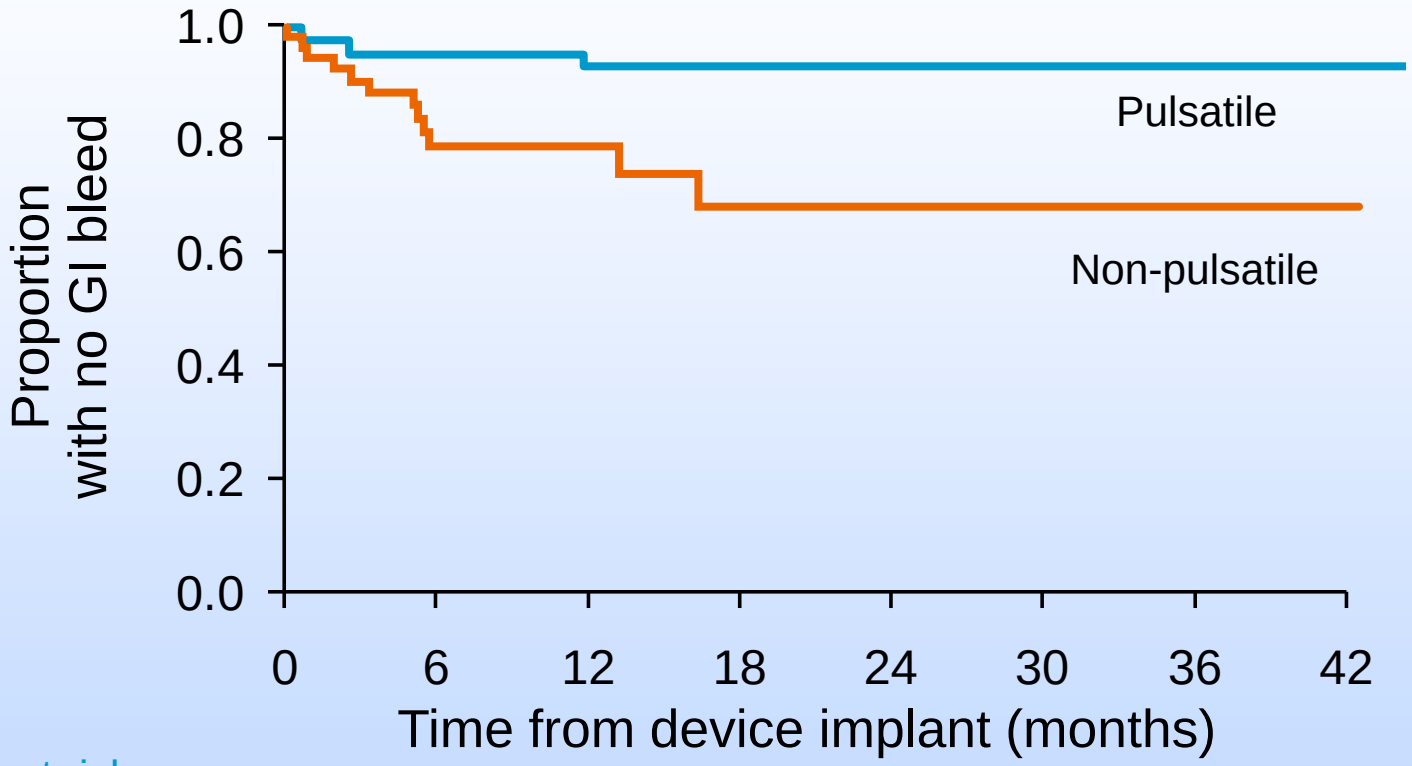
Post-LVAD GI Bleeding Events



No. at risk

Pulsatile	46	40	28	12
Non-pulsatile	55	23	6	2

Crow et al: JTCVS, 2009

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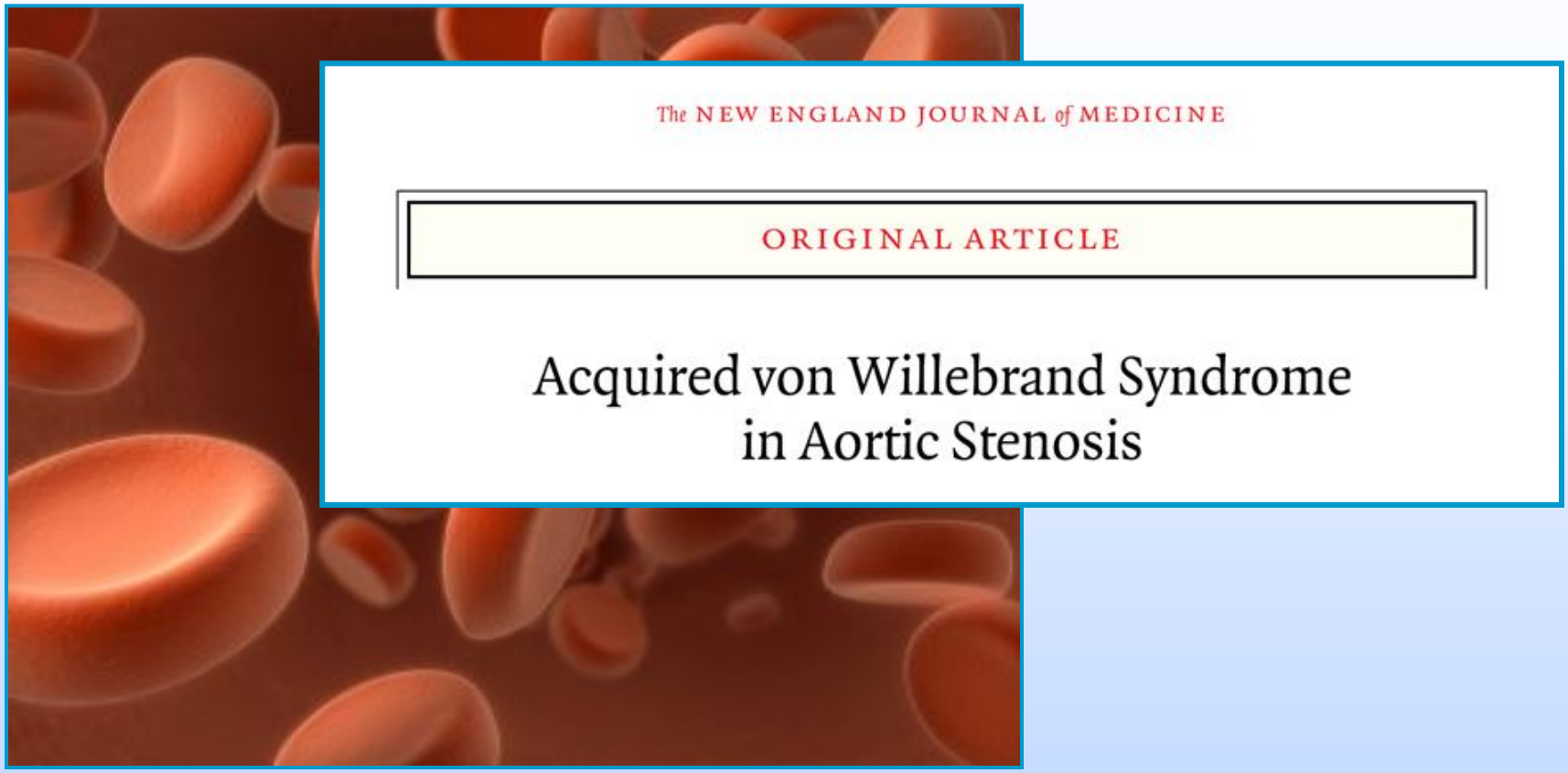
Acquired von Willebrand Syndrome



The link between aortic stenosis and gastrointestinal bleeding

Vincentelli et al: NEJM, 2003

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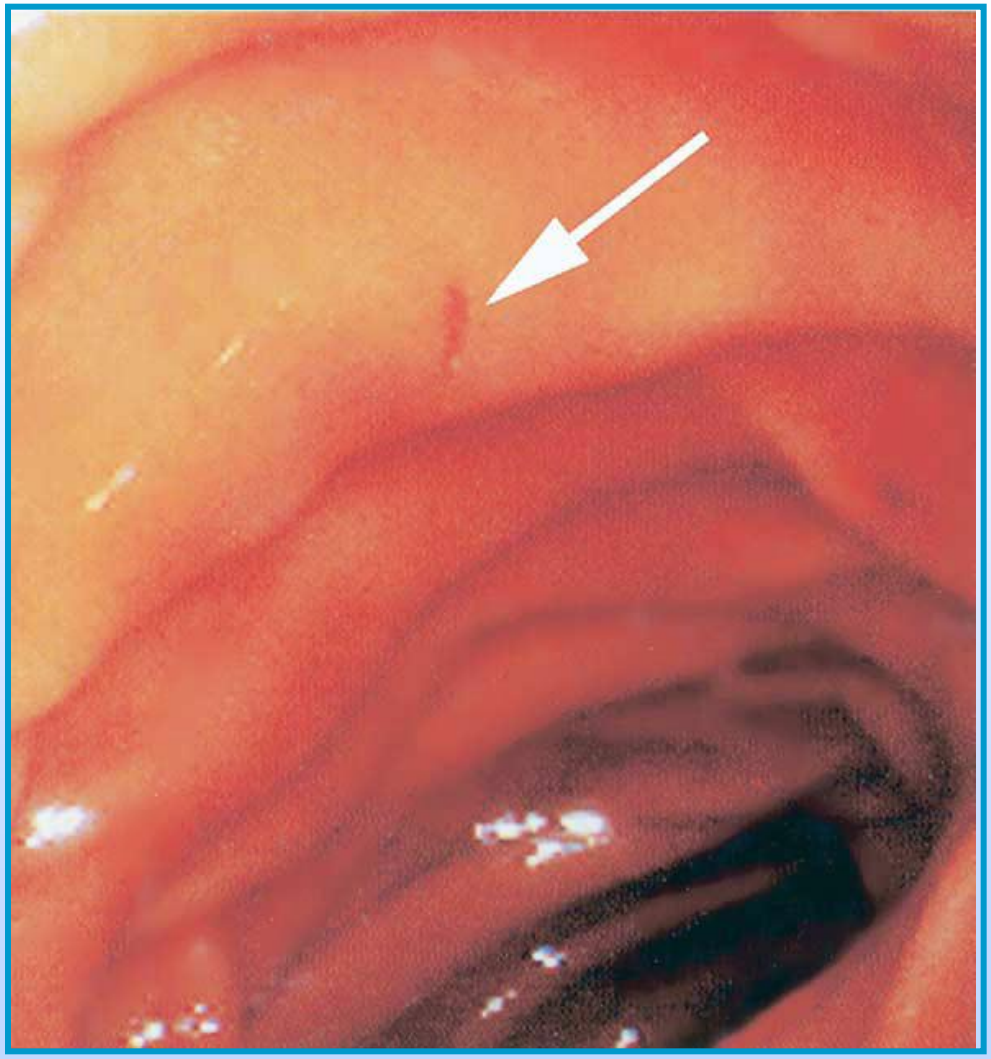
Ileal AVM with Bleeding



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Acquired von Willebrand's Disease

- Common characteristic in pts with AS and CF-VADs: reduced pulse pressure
- Results in
  - Dilatation of the mucosal veins
  - Increased smooth muscle relaxation
  - Arterio-venular dilatation
  - Arteriovenous malformation
  - Bleeding

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Acquired von Willebrand's Disease

- HMW multimers of vWF necessary for proper platelet adhesion and aggregation
- Deficiency occurs in AS when high shear stress increases proteolysis passing through the stenotic aortic valve

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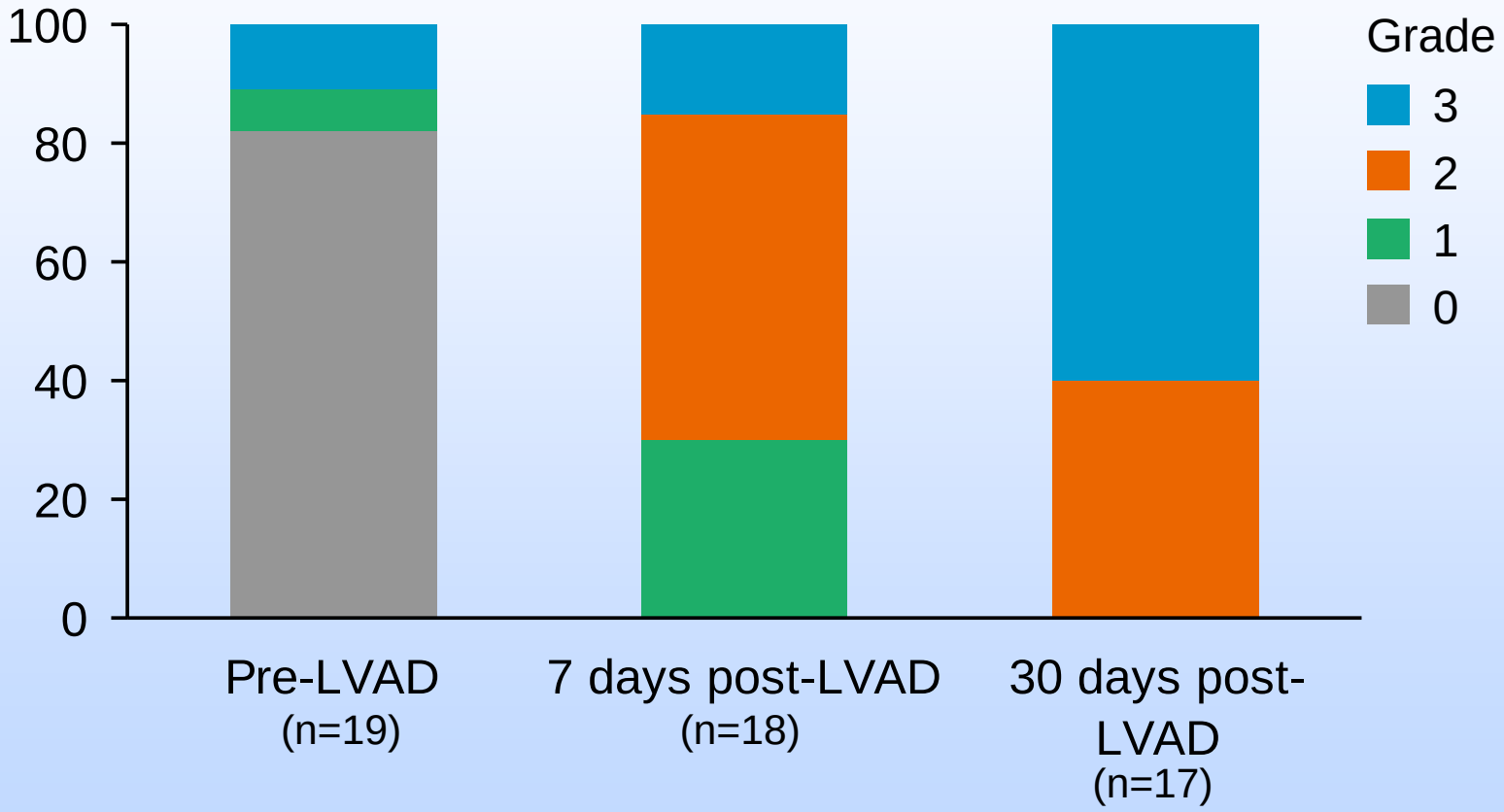
HMW Multimer Deficiency



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Bleeding Events

- Ten patients (27%) of the 37 experienced bleeding complications
- Sources
  - Lower GI (5)
  - Epistaxis (4)
  - Intracranial (1)
- Median time from implant to bleed = 22 days

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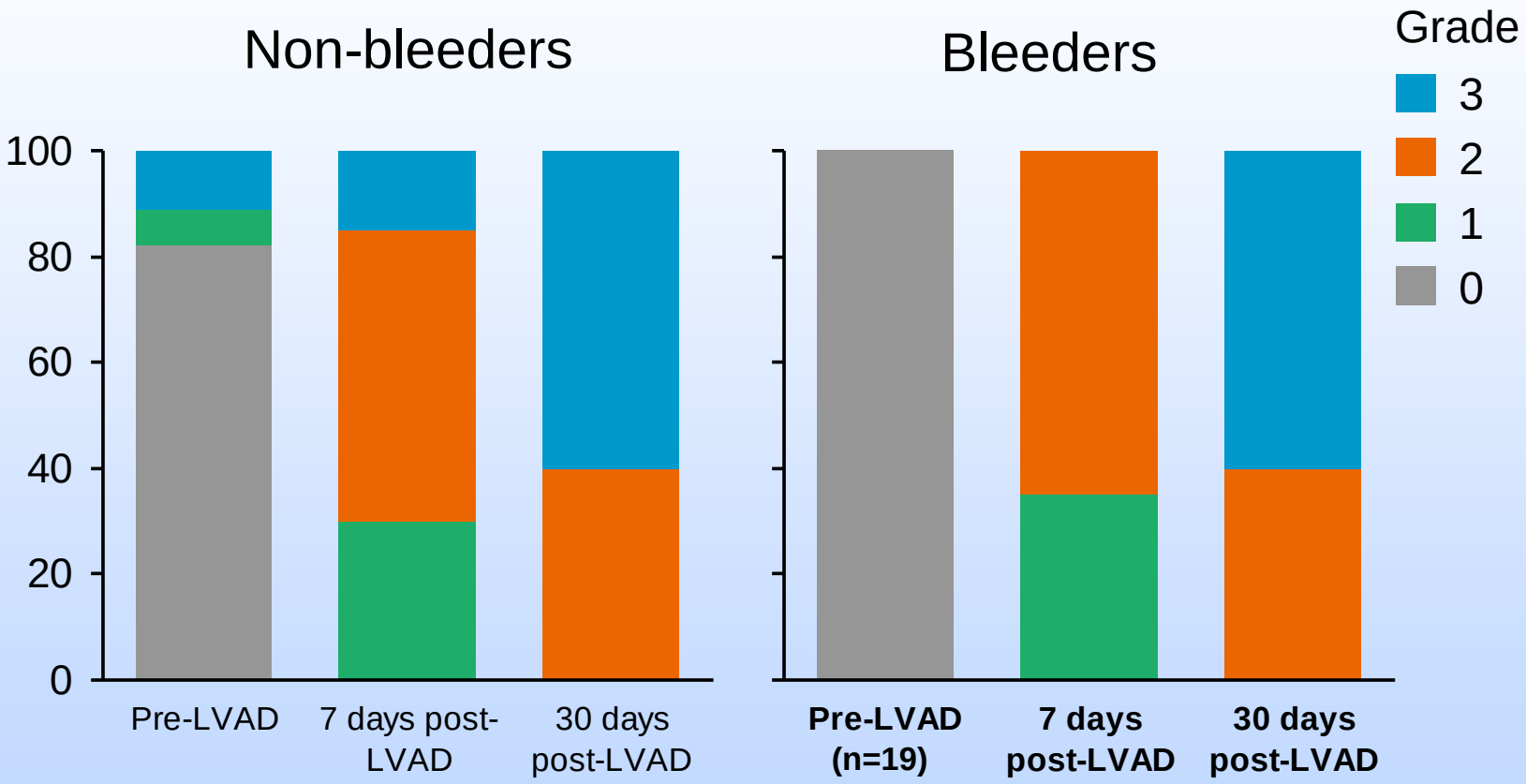
HMW Multimer Deficiency



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Conclusion

- All HeartMate II recipients tested developed HMW multimer loss by 30 days after implantation
- Current methods for evaluating HMW multimer loss do not differentiate bleeders from nonbleeders
- Additional exploratory analysis is needed to identify predictors of bleeding risk in LVAD recipients

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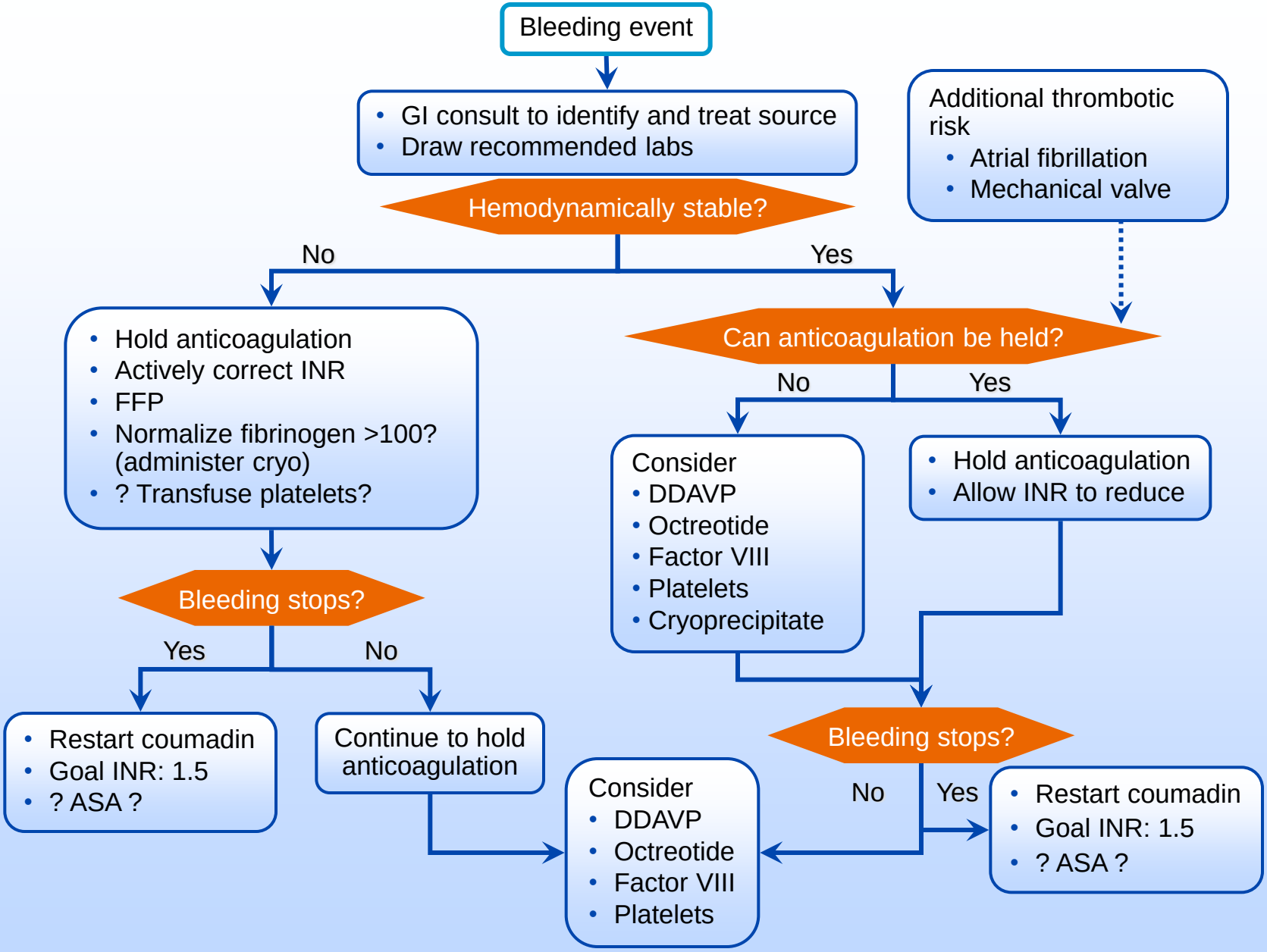

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Treatment of GI Bleeding

- Based on findings
- Treat anemia – oral Iron or transfusion
- AV malformations – thermocoagulation, electrocoagulation, photocoagulation
- Vasopressin infusion
- Bowel resection

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Treatment of GI Bleeding

- Hematologic assessment
- Antifibrinolytics and vWF replacement when von Willebrand's disease confirmed
- Decrease LVAD pump speed to decrease shear stress and further depletion of HMW vWF

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Take Home Points

- Increased hemolysis could be due to:
  - thrombus in pump or inflow cannula
  - Shift or malposition of inflow cannula
- Most GI bleeding in HM II thought to be due to HMW vWF multimer loss
- Treat based on findings
- Consider decrease in pump speed to decrease shear stress

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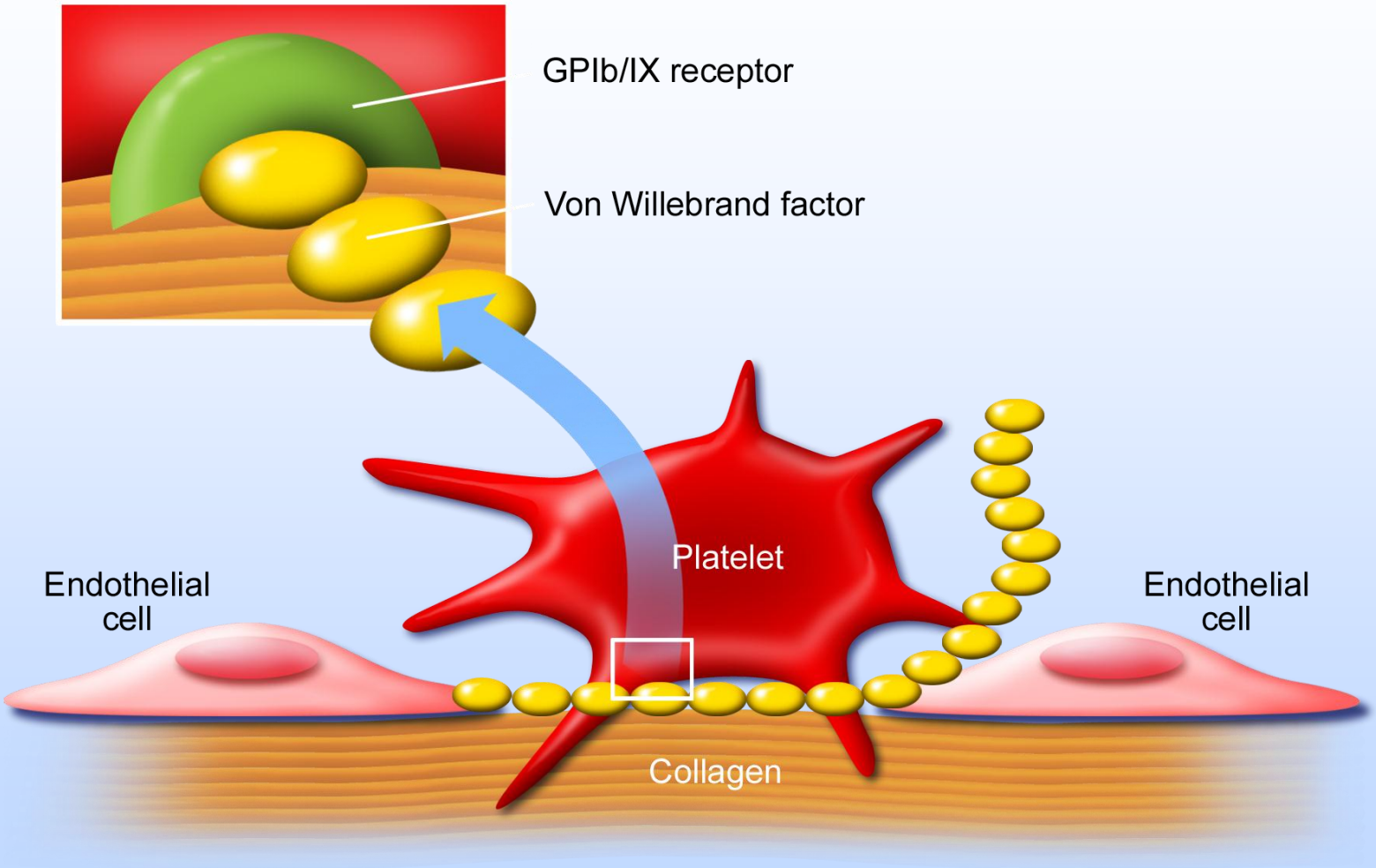
vWF Factor



Large Multimeric Protein > 20,000 KD

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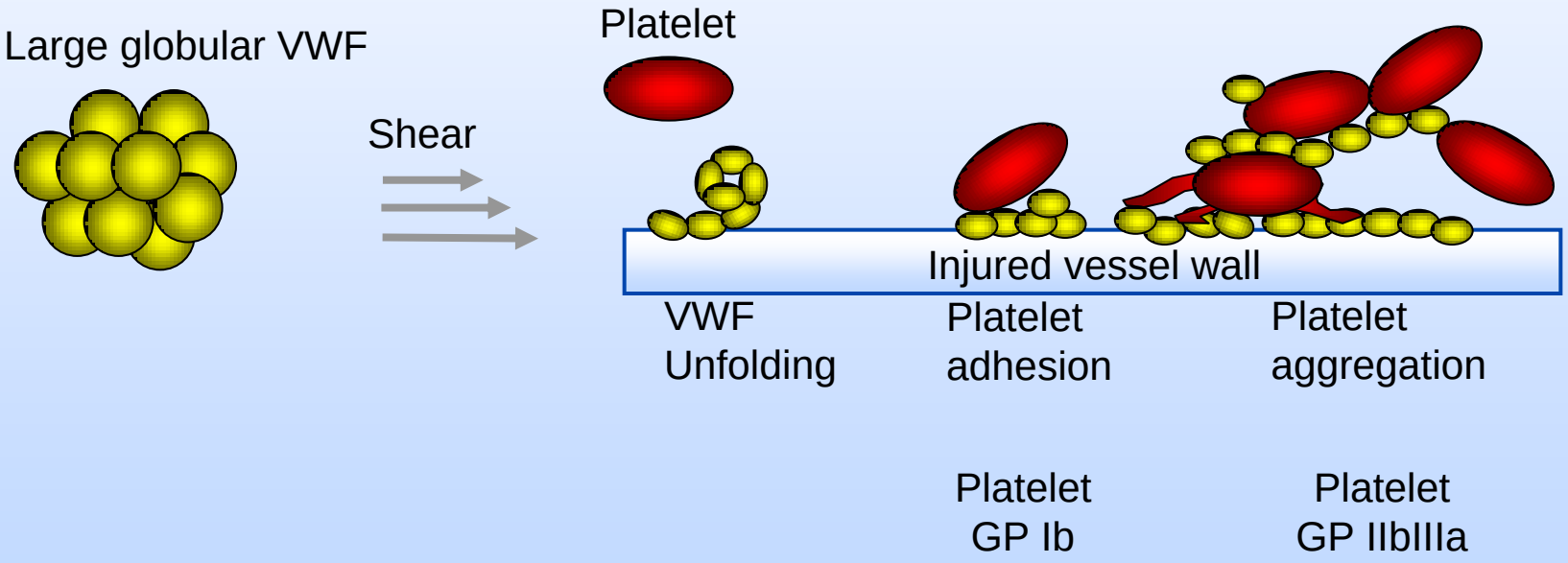
Von Willebrand Factor
Platelet Rolling and Adhesion



Mannucci PM: NEJM 351:683, 2004

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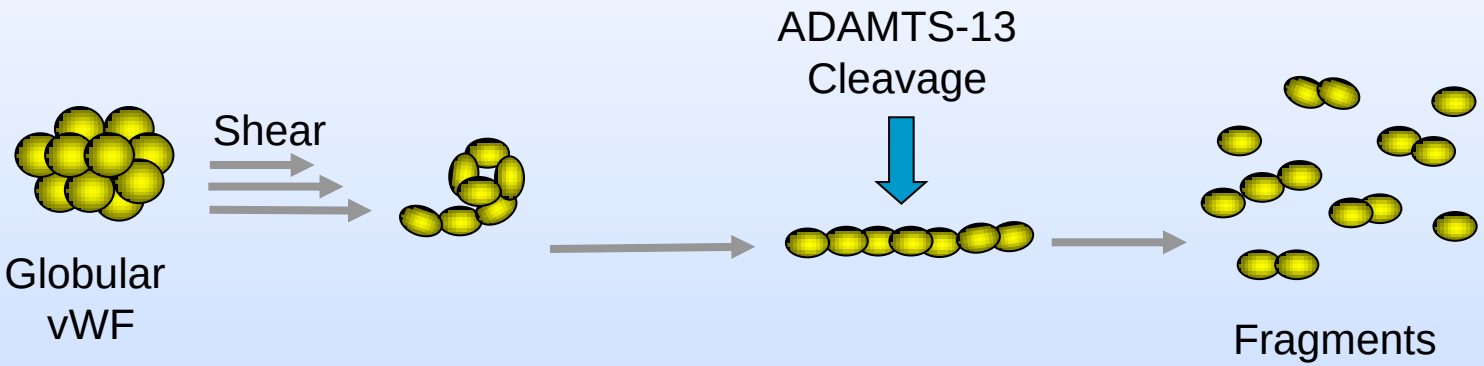
Von Willebrand Factor
Catabolism by ADAMTS-13



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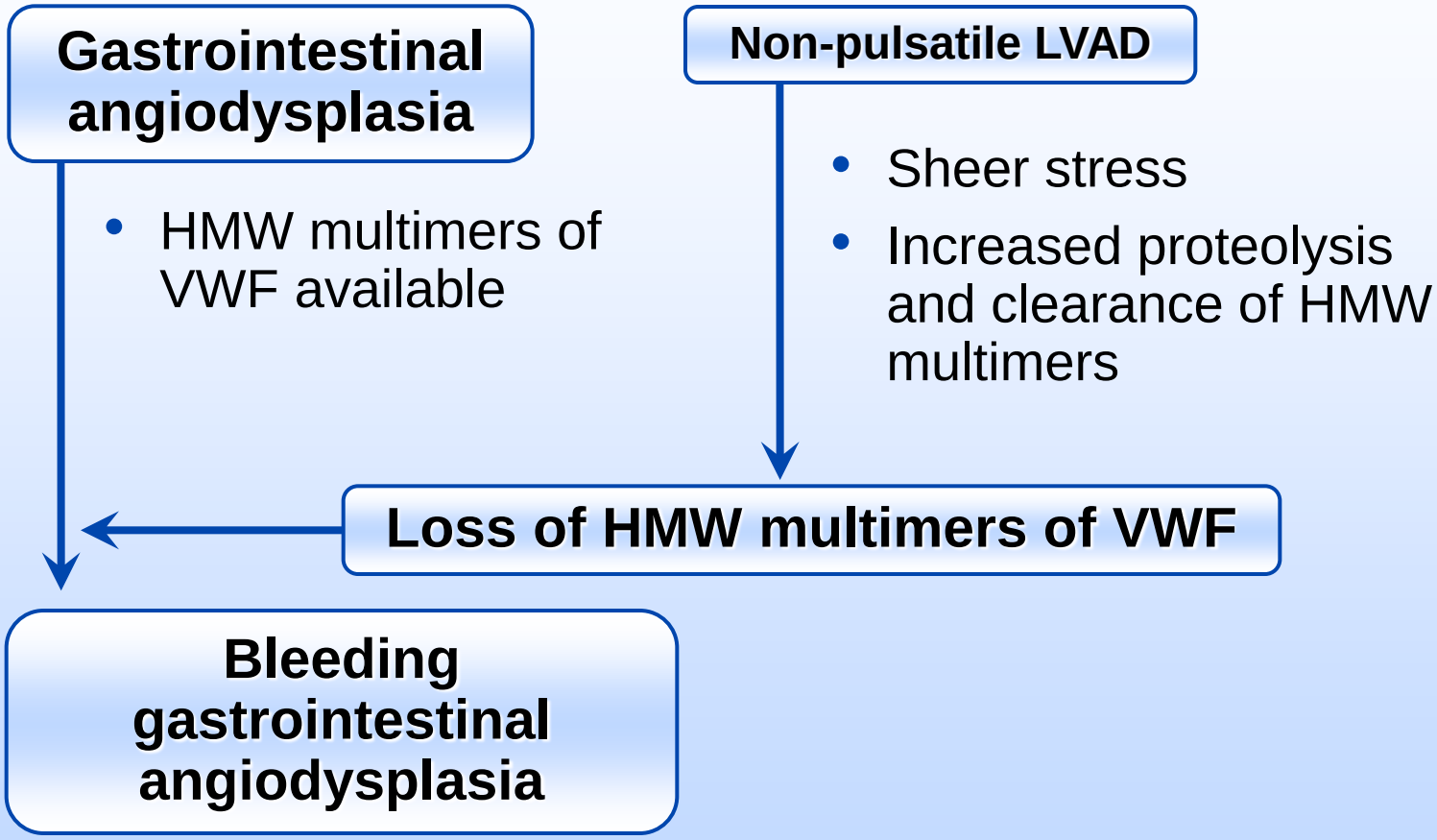
Non-Pulsatile LVAD and GI Bleeding



Warkentin et al: Transfusion Medicine Reviews 17: 272, 2003

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Adverse Events (1 of 2)

Adverse event	Pt (n=281) No.	%
Bleeding: requiring re-exploration	72	26
Infection		
Local non-device related	84	30
Sepsis	49	17
Device related: percutaneous lead/ (pump pocket)	37 (5)	13 (2)
Ventricular arrhythmias: cardioversion/ defibrillation	56	20
Renal failure	30	11

Pagani et al: JAAC 54, 2009

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Adverse Events (2 of 2)

Adverse event	Pt (n=281) No.	%
Bleeding: requiring re-exploration	72	26
Infection		
Local non-device related	84	30
Sepsis	49	17
Device related: percutaneous lead/ (pump pocket)	37 (5)	13 (2)
Ventricular arrhythmias: cardioversion/ defibrillation	56	20
Renal failure	30	11

*Use of RVAD or extended inotrope use ≥14 days or starting after 14 days

Pagani et al: JAAC 54, 2009

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Serious Device Events – Malfunctions

LVAD replaced (n=12, 4.3%)
4 device thrombosis (including 2 deaths)
4 percutaneous lead wire damage
3 complications of surgical implantation
1 percutaneous lead/pump pocket infection

LVAS-related deaths (n=7, 2.5%)
4 internal components
- 2 device thrombosis
- 1 outflow elbow disconnect
- 1 inflow graft twisted

3 external components/patient related
- 2 batteries depleted or incorrectly replaced
- 1 accidental percutaneous lead trauma

LVAD pump mechanical failure: 0

Pagani et al: JAAC 54, 2009

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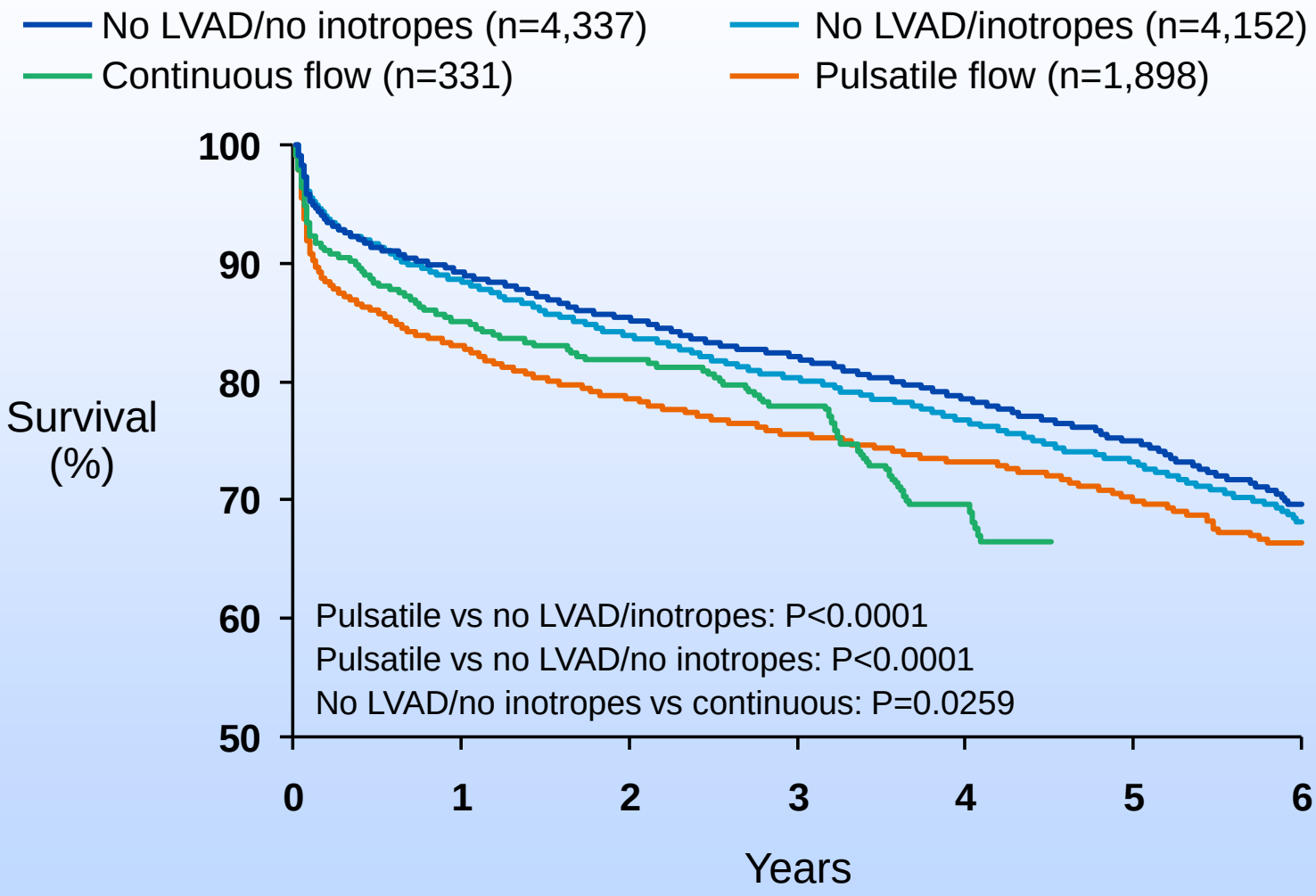
LVAD and Post-Transplant Outcome



Taylor: JHLT, 2009

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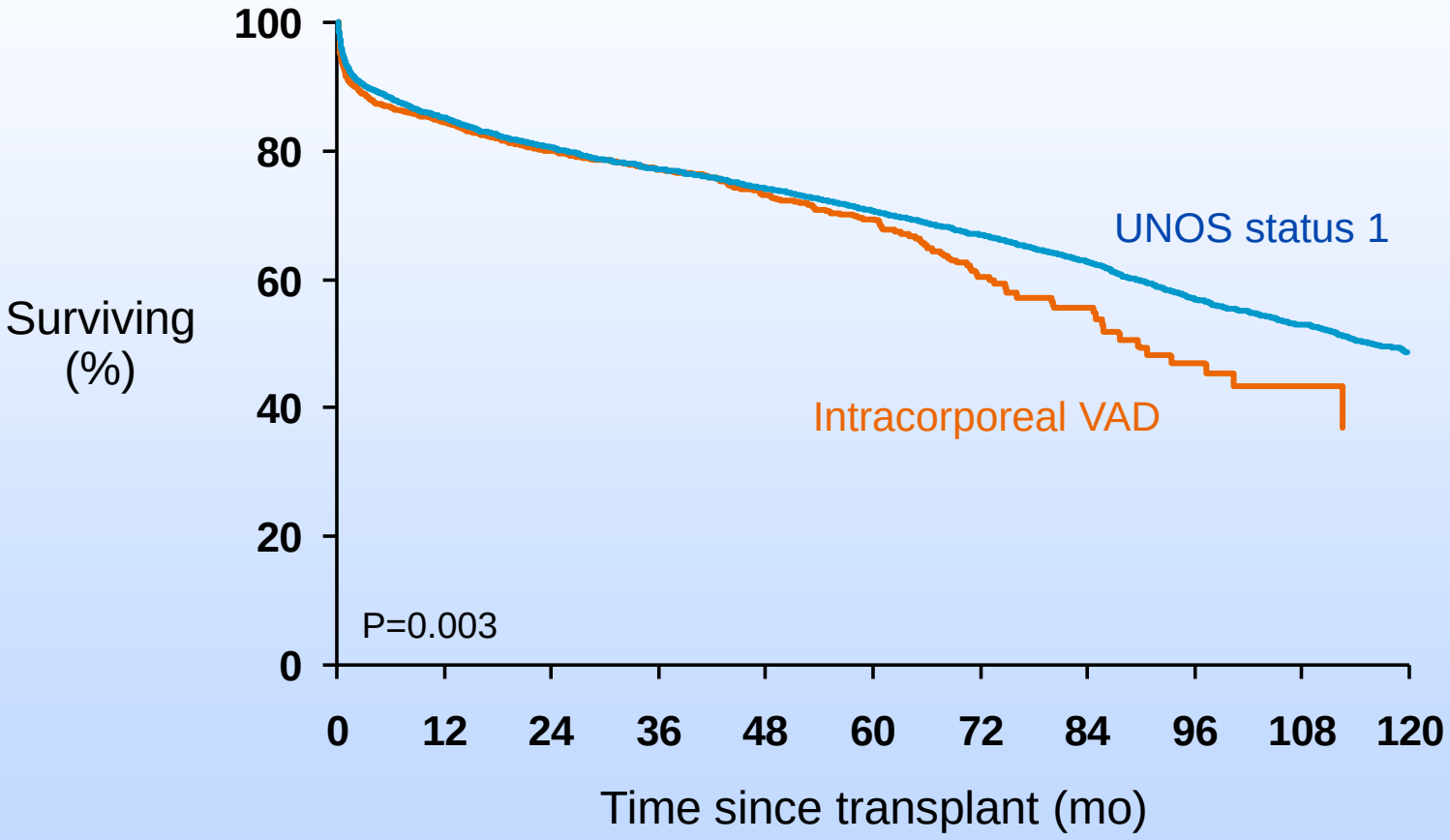
Post-Transplant Mortality – UNOS



Patlolla, 2009

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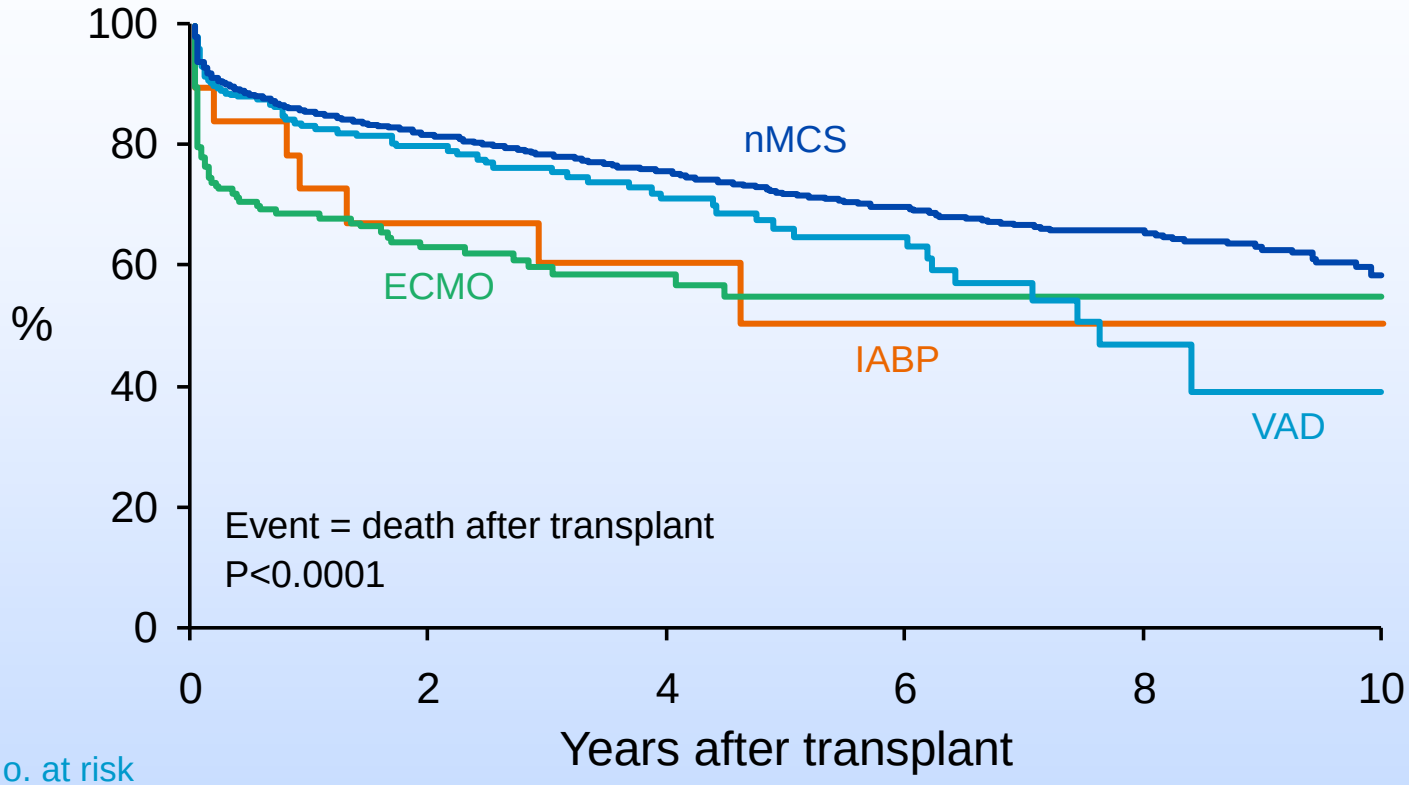
Pediatric Patients – UNOS



No. at risk

nMCS	2,073	1,199	771	442	209	36
VAD	241	125	72	42	7	1
ECMO	171	73	36	20	7	2
IABP	19	12	6	3	1	1

Davies, 2008

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Redo Sternotomy

Demanding procedure

- Operation time increased
- Cardiopulmonary time increased
- Ischemic time increased
- Transfusion increased

Massad et al: JTCS, 1996; Cleveland et al: JTCS, 2008; Fernandez et al: JHLT, 2005

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Effect of LVAD on PRA

Pretransplant PRA in Patients with/Without LVAD

	LVAD	Control	P
PRA at listing	4.1±13.0	2.0±6.1	0.4
Max PRA before transplant	29.8±36.1	3.1±10.6	<0.001
Min PRA between listing and transplant	10.9±20.5	1.1±4.3	0.023
PRA prior to transplant	16.2±27.5	2.1±8.5	0.015

Sasaki, 2009

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Effect on PVR

- Increased PVR is an incremental risk factor for early and late death after heart transplantation
- LVAD therapy has been shown to reduce PVR
- Now considered appropriate to consider LVAD prior to transplant in pt with elevated PVR

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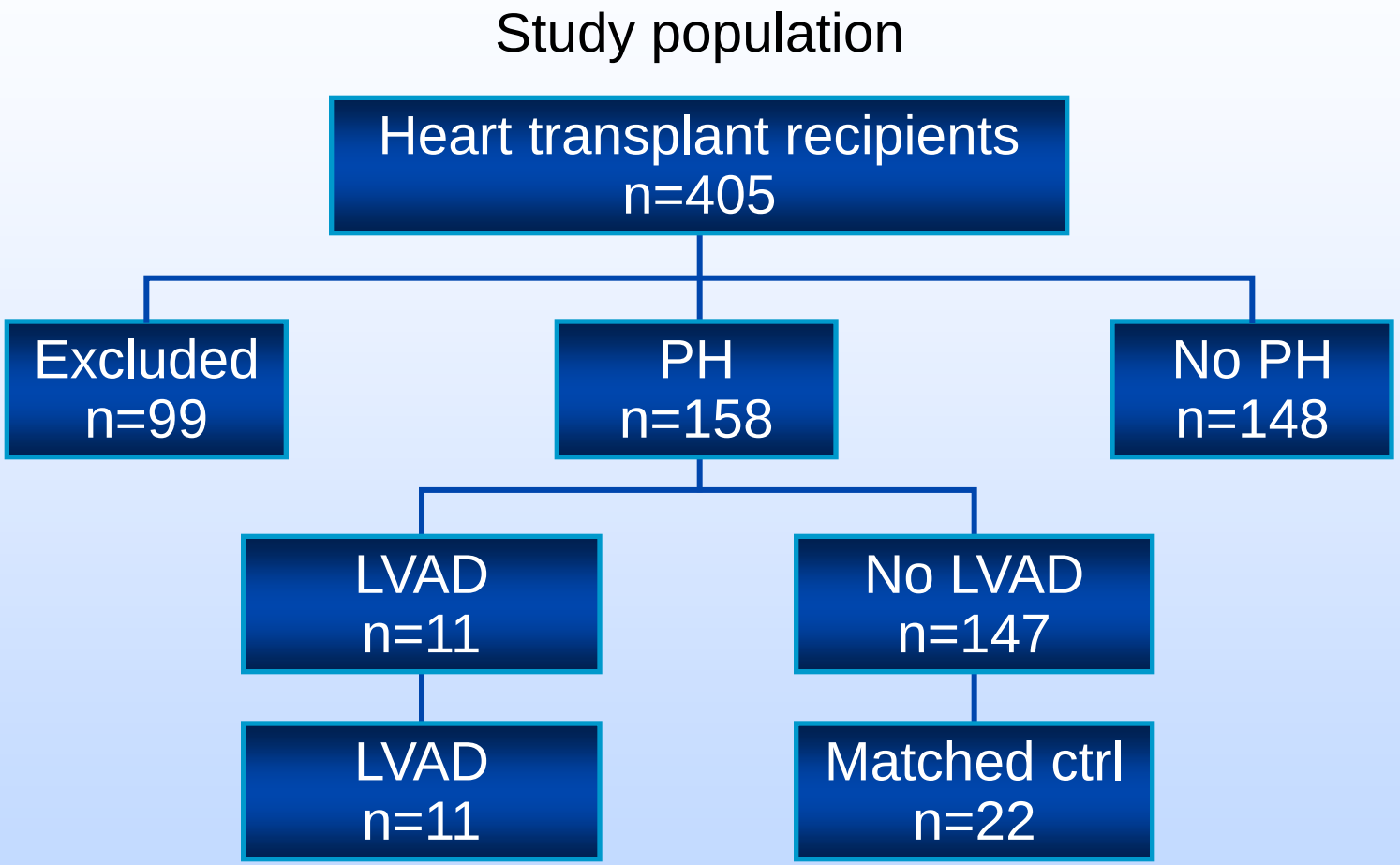
PVR and Post-Transplant Survival



22 pt with PH were matched to 11 pt with PH pretreated with LVAD
Liden, 2009

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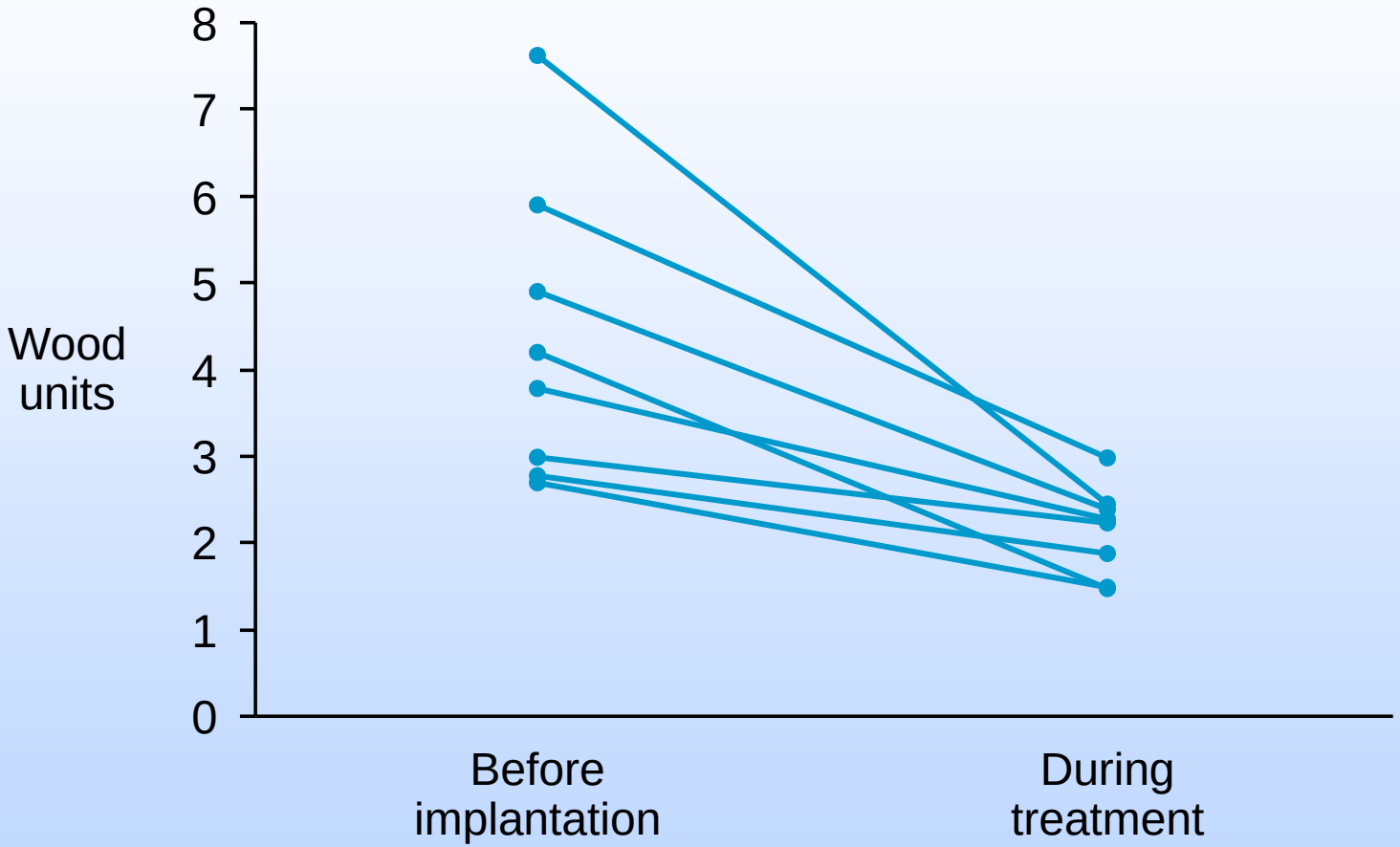
PVR After LVAD



Liden, 2009

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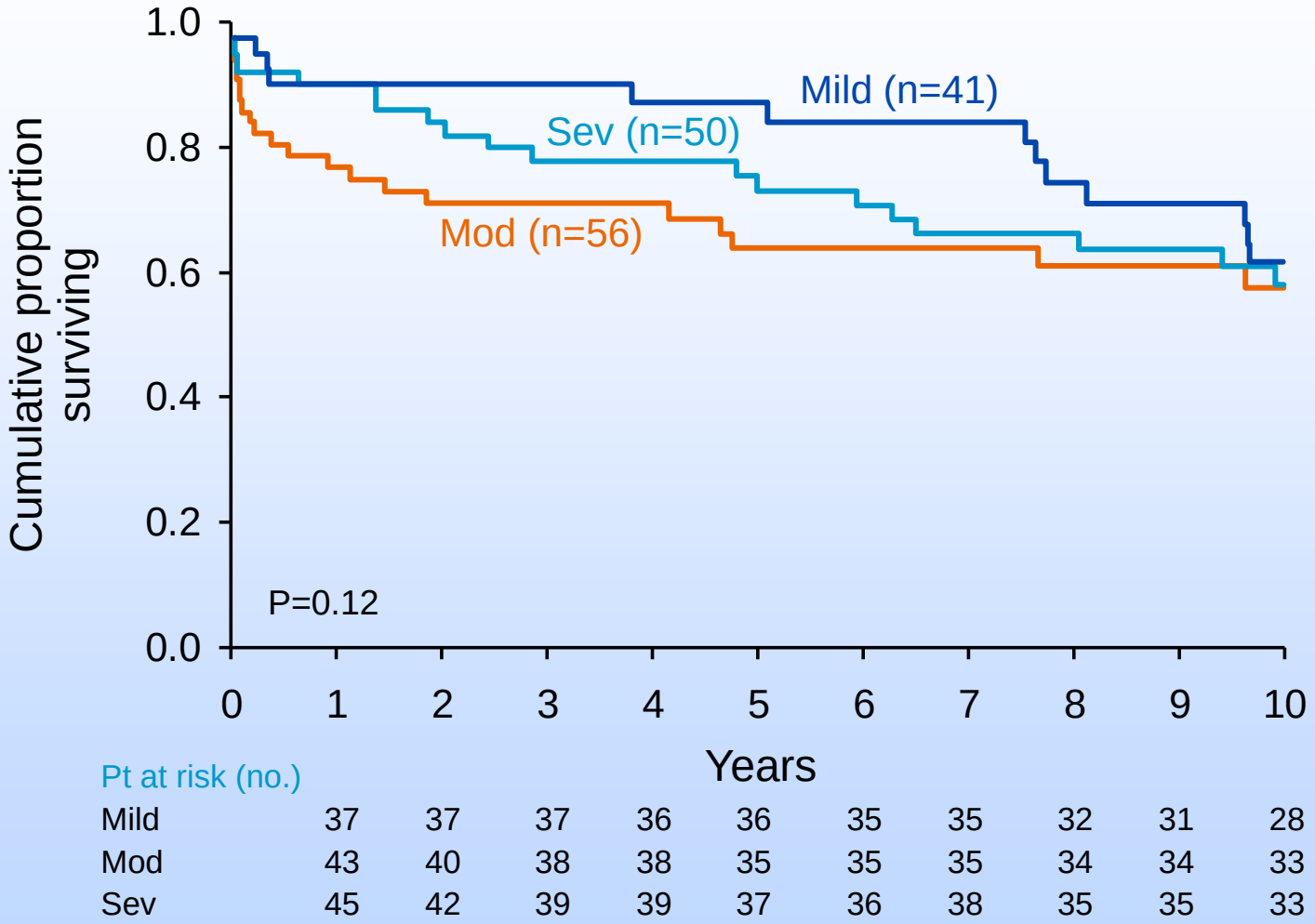
Survival Related to PVR



Liden, 2009

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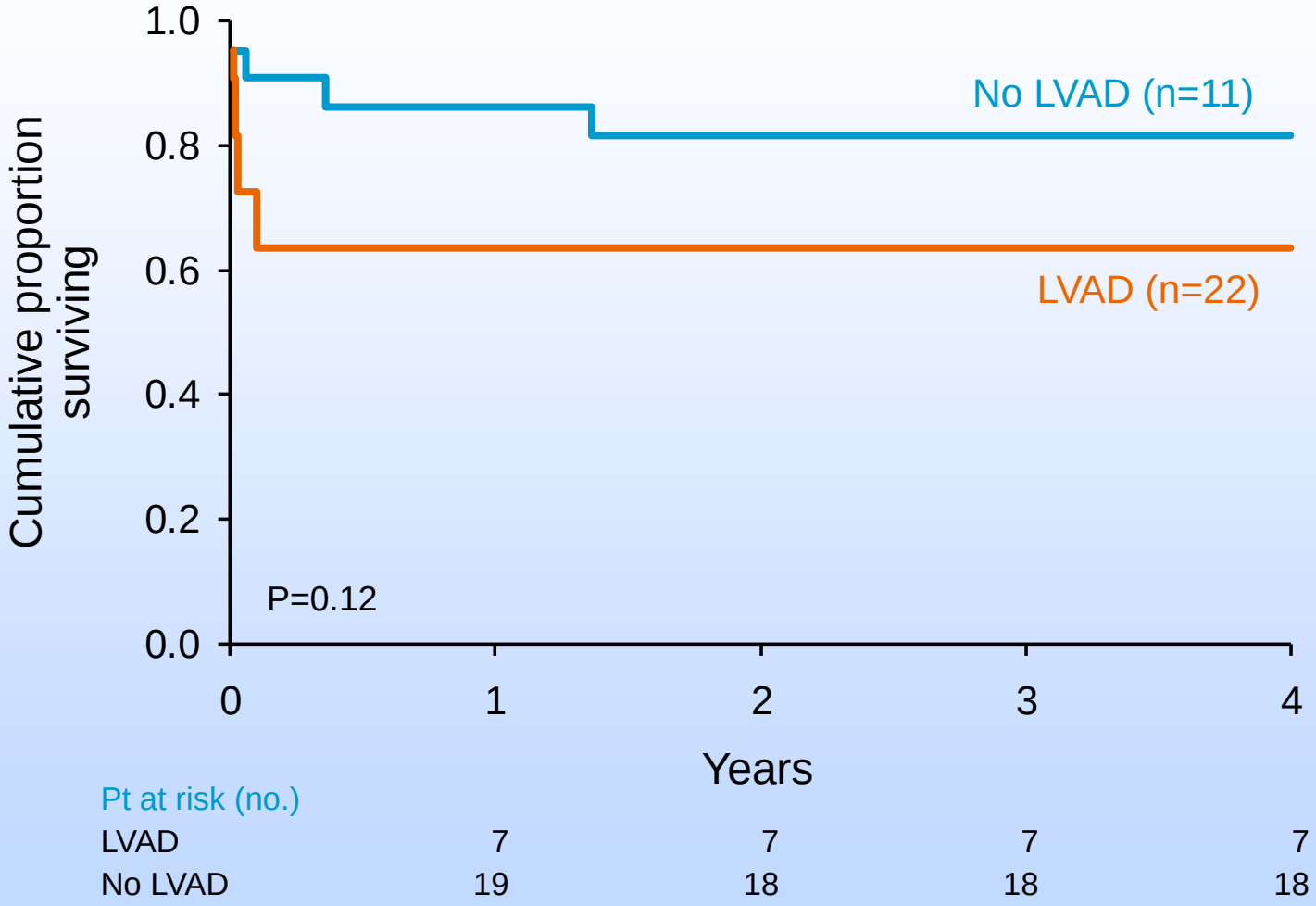
Influence of LVAD



Liden, 2009

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Mayo Experience

2007-2009

Age >18 years

Group I

LVAD with continuous flow pumps

Purpose of LVAD – BTT

Group II

UNOS status I

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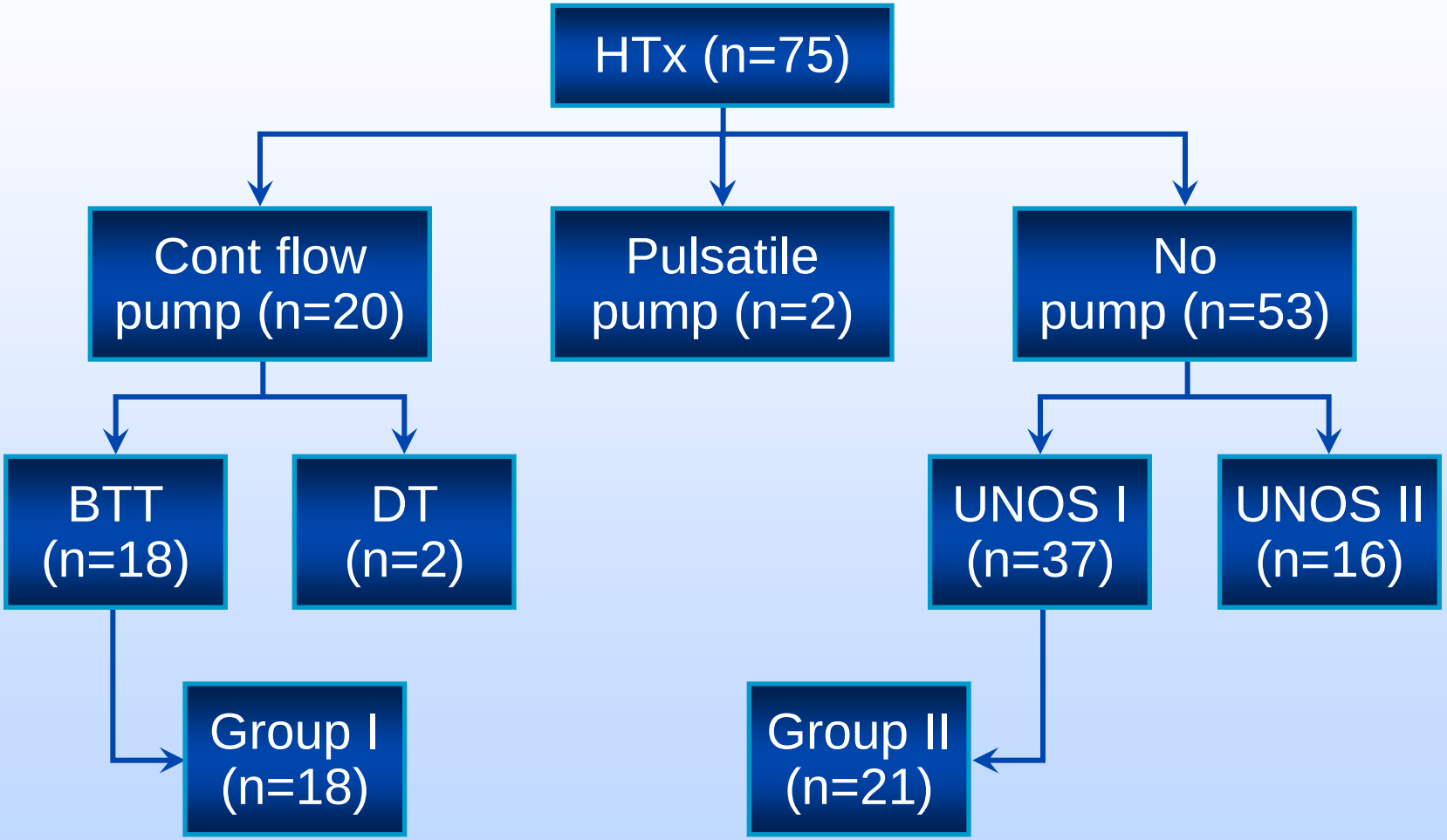
Mayo Experience



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Baseline Characteristics

Variables	Group I (n=17)	Group II (n=21)	P
Age	50±12	52±11	0.5794
Female	4	10	0.1258
BSA	2.02±0.24	1.90±0.25	0.1472
Blood group O	4	7	0.5076
Blood group Rh-	3	3	0.7775
Ischemic/nonischemic	6/11	7/14	0.8992
IABP	5	0	0.0077
Hemodynamics			
Systolic BP	96±12	106±14	0.0287
Diastolic BP	64±10	65±11	0.6700
Mean BP	71±8	75±11	0.2704
Heart rate	82±16	80±16	0.5662
Echocardiography			
Ejection fraction (%)	17±4	26±15	0.0065
LVIDD (mm)	72±13	62±17	0.0494
MR III or IV	9	10	0.7442

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Variables	Group I (n=17)	Group II (n=21)	P
Catheterization			
Mean PA pressure	35±10	34±10	0.8930
RAP	12±5	16±7	0.1115
PCWP	24±7	21±8	0.3602
Cardiac output	3.4±1.2	3.5±1.2	0.7389
Cardiac index	1.6±0.4	1.9±0.6	0.3091
PVR (wood unit)	3.9±1.7	4.2±2.4	0.9867
Exercise test			
VO_2max	11±3	10±2	0.6511
Predicted VO_2max	32±8	36±8	0.1635
Blood test			
Hemoglobin	12.0±1.9	12.1±1.7	0.8227
Serum creatinine	1.1±0.2	1.1±0.3	0.8453
AST	32±12	50±76	0.4446
Serum albumin	3.6±0.7	4.3±0.5	0.0031
Total bilirubin	1.4±1.1	1.0±0.7	0.7349
Direct bilirubin	0.5±0.5	0.4±0.3	0.4667
LDH	294±110	202±20	0.1093
BNP	1,436±957	759±687	0.0077

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Follow-Up Results

Duration

- Group I: 352±214 days (range 23-738)
- Group II: 443±73 days (range 30-1,039)

Deaths

- Group I (n=2)
  - Cardiac tamponade after 1 m
  - Septic shock after 18 m
- Group II (n=2)
  - Septic shock after 7 m
  - Unknown after 15 m

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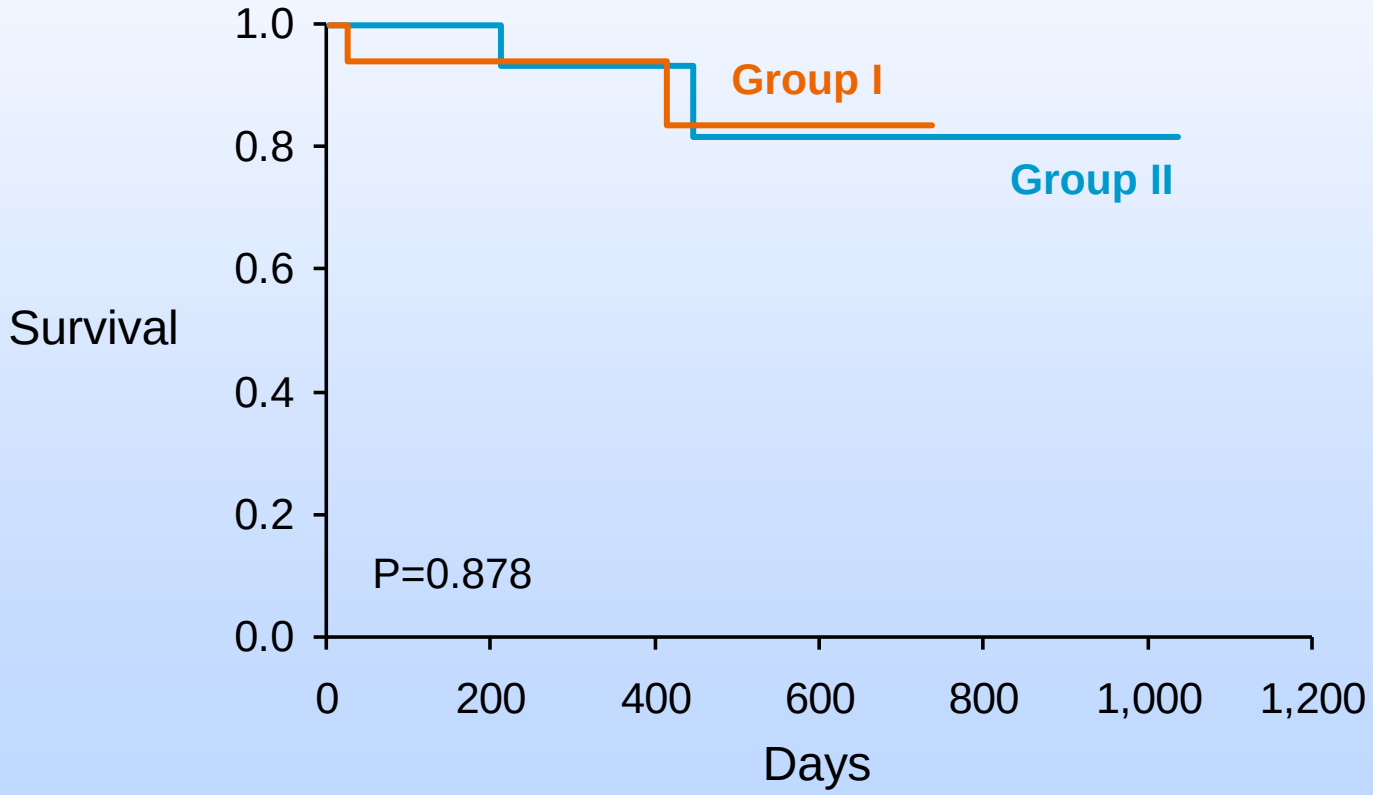
1-Year Survival Rate

- Group I 94.1±5.7%
- Group II 93.3±6.4%



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Evidence for Benefit?

Careful selection mandatory

Potential morbidity

- Complex operation
- Risk of infection
- Sensitization
- GI bleeding
- Cerebral bleeding

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Is Earlier LVAD Better?

- Pt who are unstable on maximal therapy may require LVAD as BTT
- End organ function can be improved by LVAD therapy
- LVAD therapy does not appear to improve post-transplant survival
- If a pt is stable on inotropic therapy LVAD implantation as BTT not justified

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