Initial Approach to the Patient With Acute Heart Failure in ICCU

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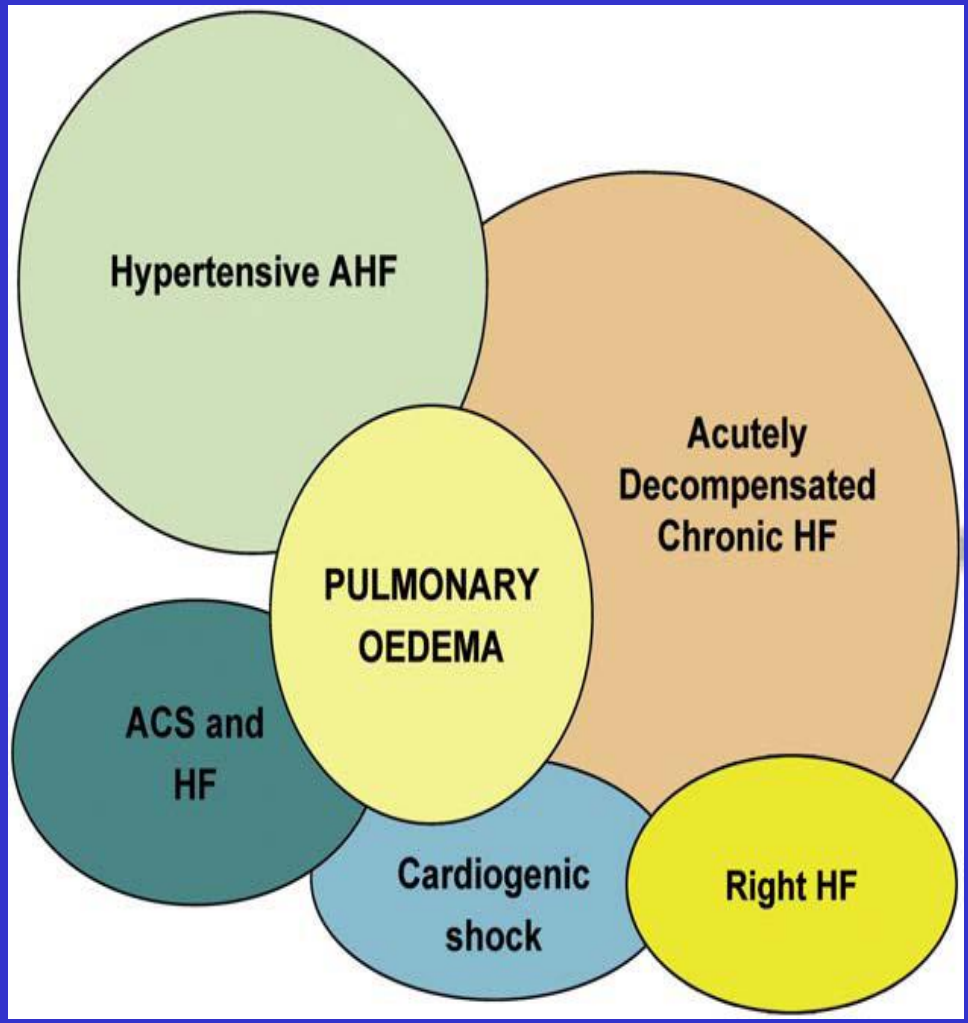
Defining AHF

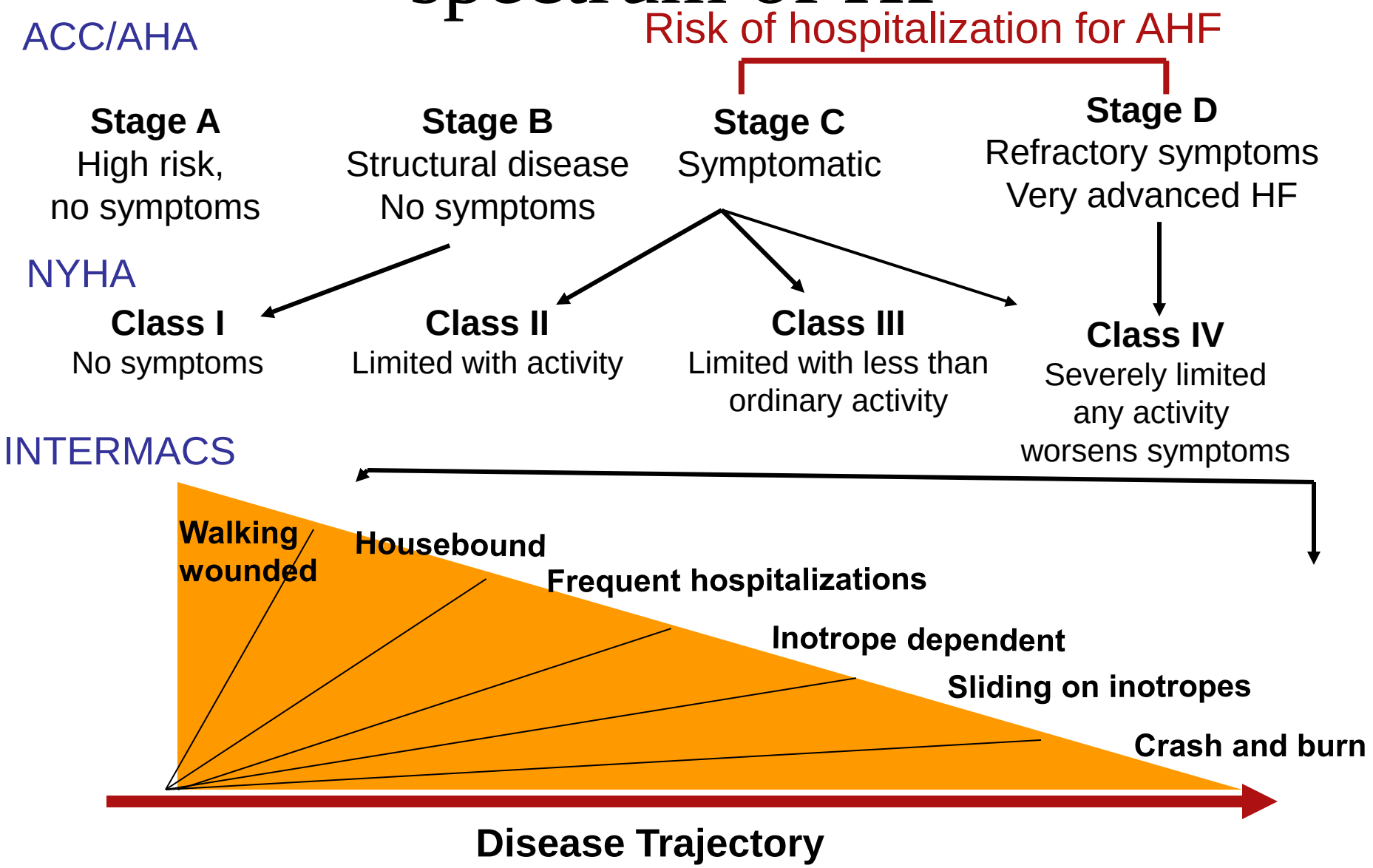
- Rapid onset or worsening of HF condition
- Results in the need for urgent therapy
- >2/3 exacerbation of chronic HF

- Variable presentation, most common are:
  - Decompensated chronic HF
  - Acute pulmonary edema
  - Hypertensive HF



Arnold JMO et al, Can J Cardiol 2007
Dickstein et al Eur J Heart Fail 2008
Nieminen MS et al Eur Heart J 2006

Acute decompensation in the spectrum of HF

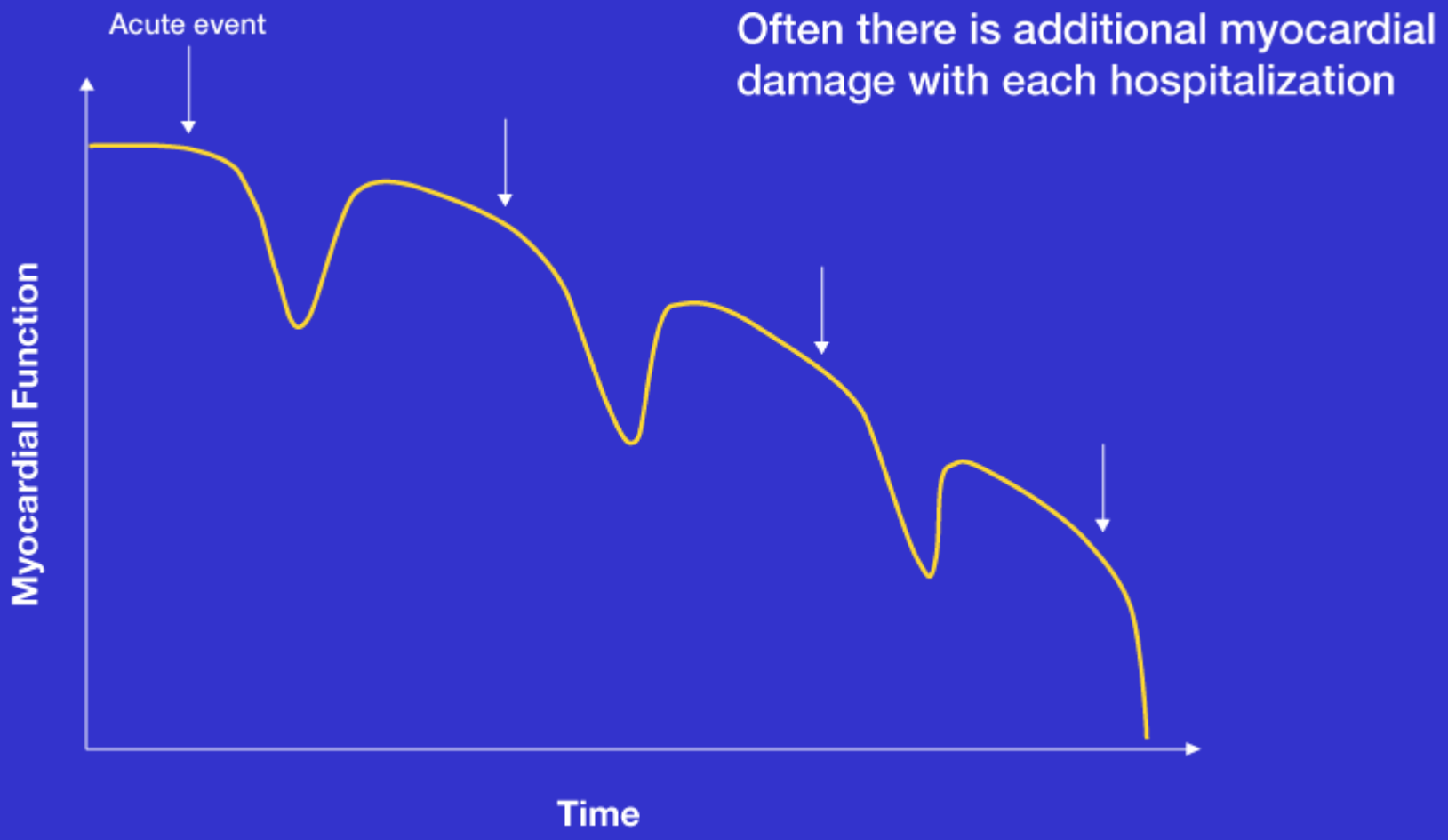


How Does AHF Present?

Characteristic	
Mean Age	72 years
Female	52%
LVEF > 40%	46%
History of Hypertension	73%
Prior MI	31%
History of DM	44%
Renal insufficiency	30%
Atrial fibrillation	31%

ADHERE Registry: N >180, 000

Cardiac Function Decreases With Each Hospitalization



Adapted from Gheorghiade M et al. *Am J Cardiol*. 2005;96:6A.

Challenges in ADHF

- Leading reason for hospital admission among patients over age 65
- Multiple comorbidities associated
- Half of the patients have preserved systolic function
- Optimal treatment remains poorly defined

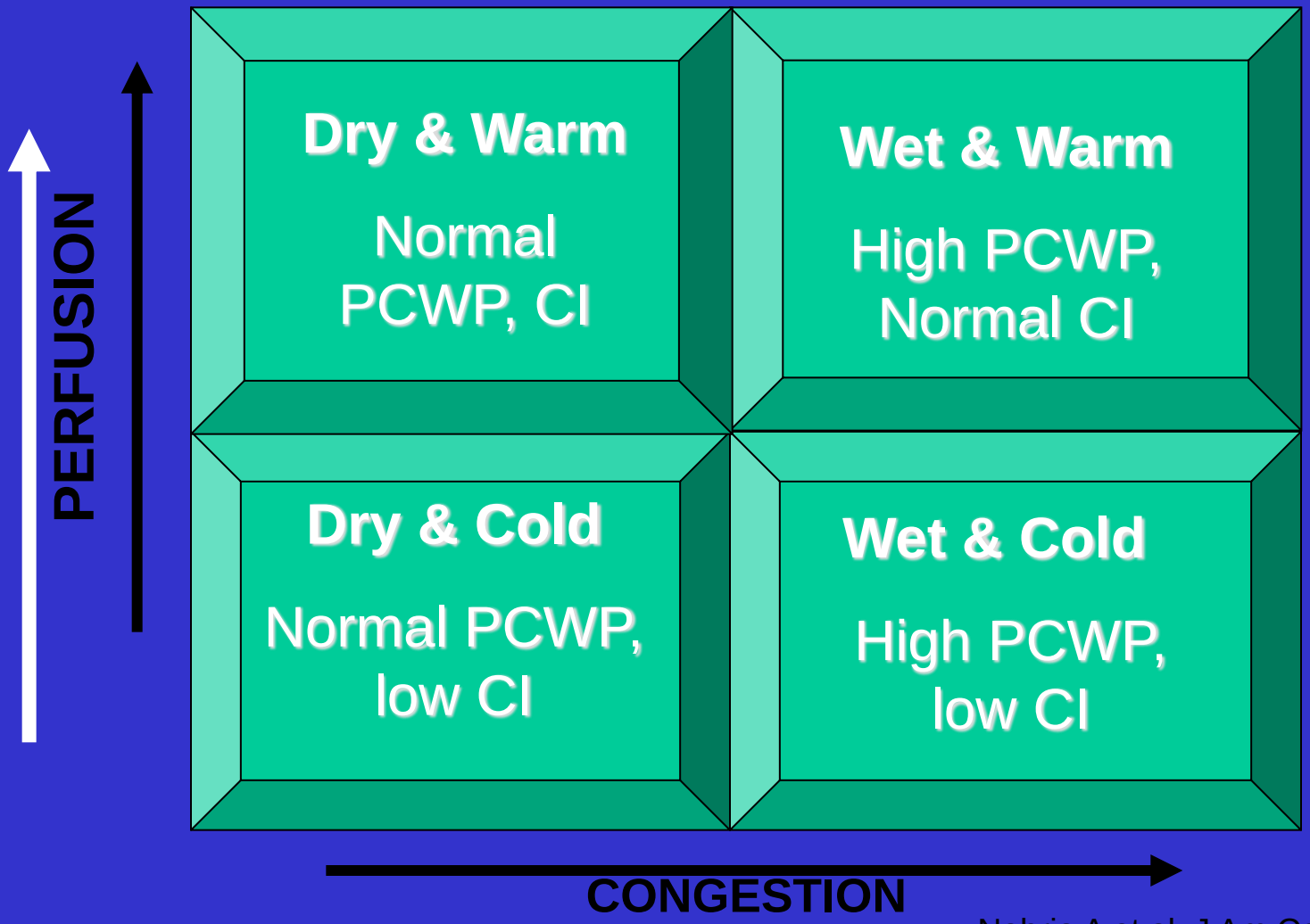
Have We Learnt To Treat ADHF?

- Therapy for ADHF has not changed significantly over the last 20 years
- Risk of death among patients admitted to hospital
  - In hospital mortality: 4 – 7%
  - 30-day mortality: 12%
  - 1-year mortality: 28%

Goals of Care

- Recognize high risk patients
- Stabilize and relieve symptoms
- Initiate therapy to improve long-term survival and prevent re-hospitalization

Risk stratification by clinical assessment



Nohria A et al. J Am Coll Cardiol 2003

Case Presentation

- 54 y/o male
- Ischemic cardiomyopathy
  - Previous MI
  - Coronary Angioplasties
  - CABG x 2
- Severe LV/RV dysfunction
  - ICD - CRT

Case Presentation

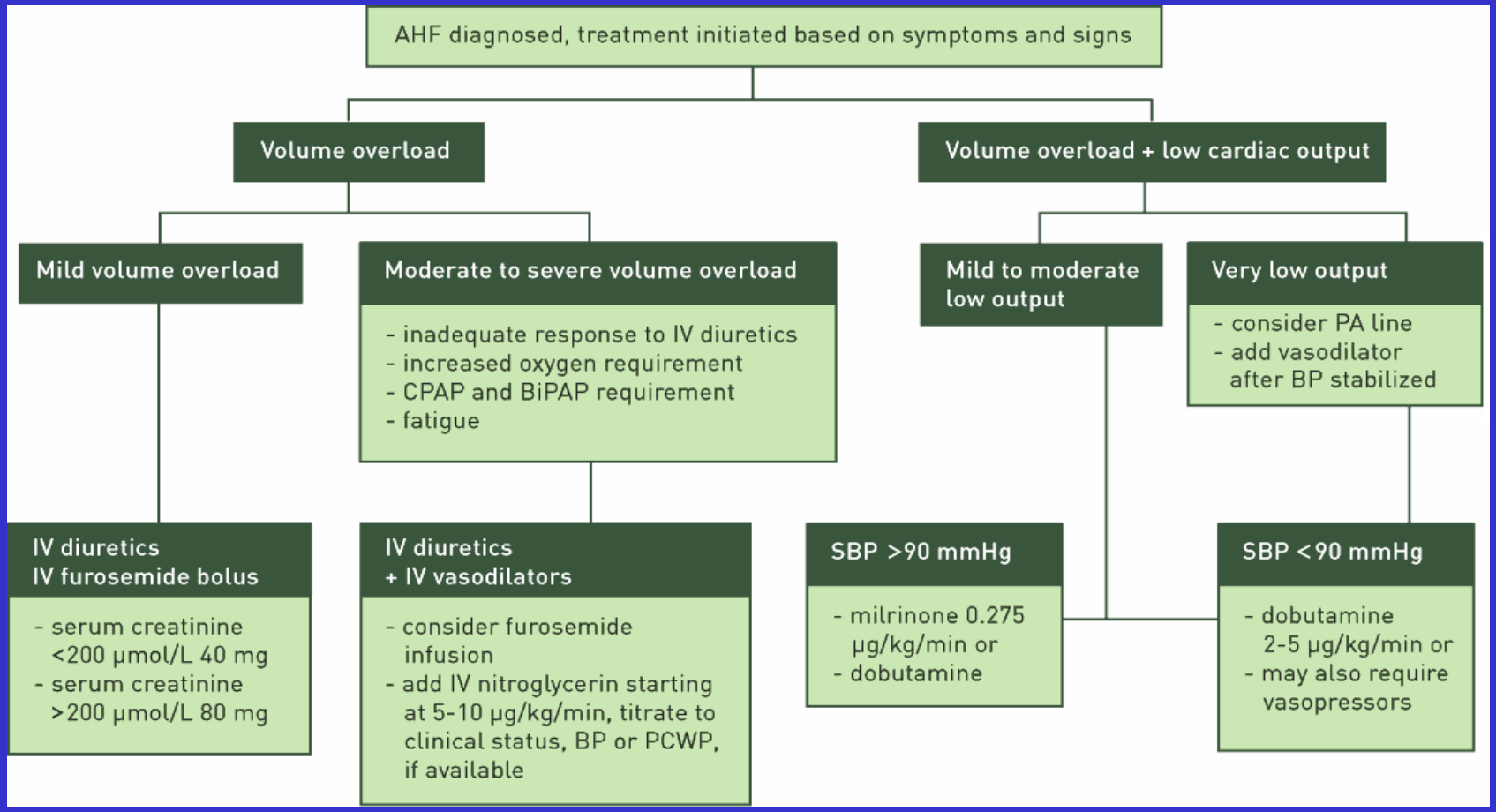
Comorbidities

- Diabetes
- Renal Dysfunction (creatinine 180)
- Liver fibrosis
- Severe pulmonary hypertension

Case Presentation

- Hemodymics
  - BP 100/ 68
  - CVP 25
  - Pu Pressures 68/36/45 wedge 28
  - CI 2.8
  - Mixed Venous 72

Treatment Algorithm



Canadian Cardiovascular Society Guidelines.

Diuresis

- Mainstay of therapy for ADHF
- Most effective therapy to reduce congestion
- No large prospective trials in ADHF

Current Diuretic Options

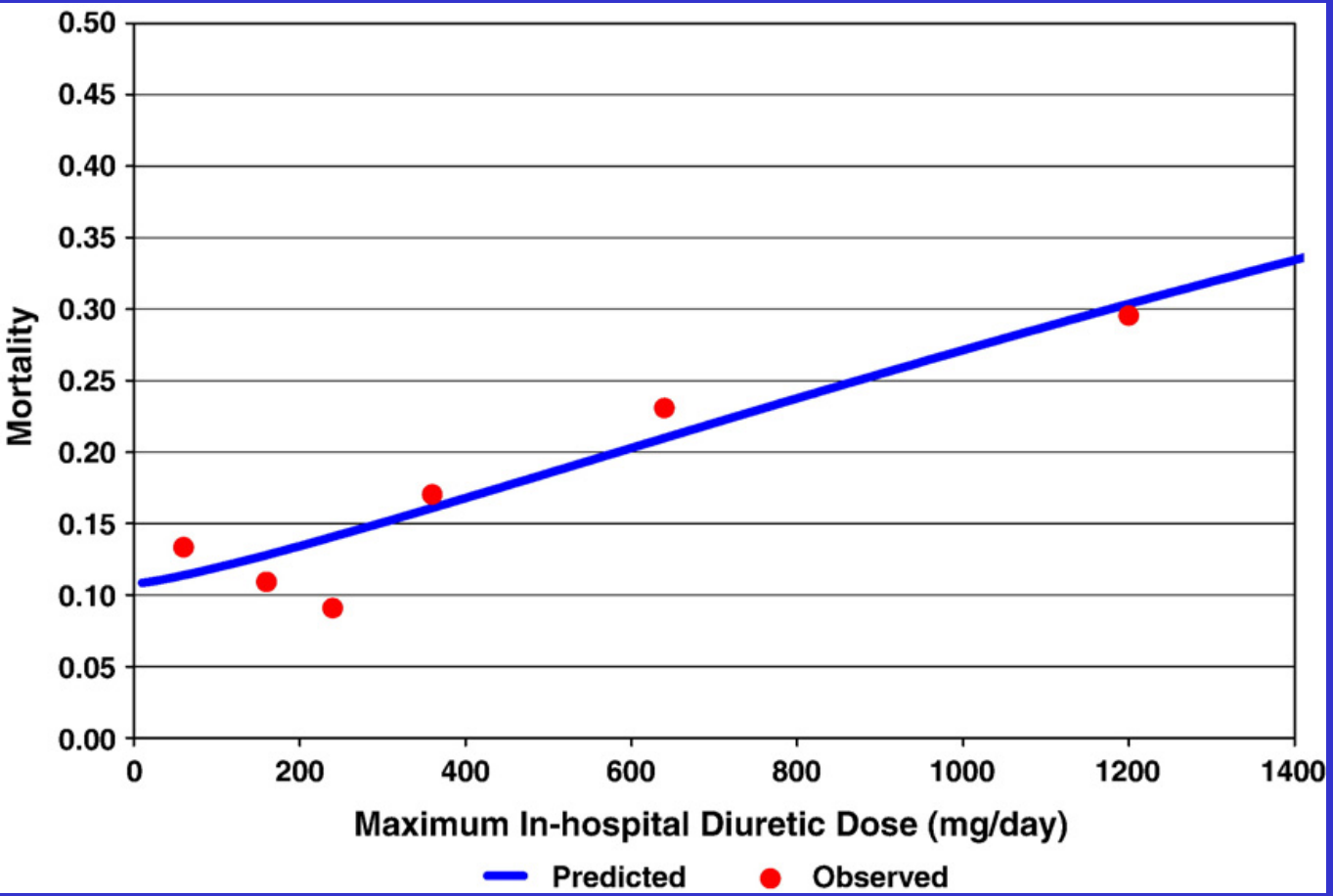
Medication	Route and dose	Indication for use	Comments
Diuretics			
Furosemide	20 mg to 80 mg oral or IV, according to symptoms	Acute diuresis in ADHF	Should be used in concert with vasoactive therapy. Usually 40 mg for every 1.5 creatinine level to max 160 mg
Bumetanide	0.5 mg to 4.0 mg oral or IV, according to symptoms	Acute diuresis in ADHF	Better absorption than furosemide in edematous states; 1:40 dose conversion with furosemide
Torsemide	10 mg to 40 mg oral or IV	ADHF	
Acetazolemide	0.5 mg oral or IV	Severe alkalosis associated with diuresis	Must closely observe creatinine and electroytes
Diuretics – refractory congestion			
Metolazone	2.5 mg to 10 mg oral	Severe refractory CHF	Potent kaliuretic: closely observe creatinine and electroytes
Furosemide	IV infusion 5 mg/h to 20 mg/h	Refractory to bolus diuretic therapy	Prolonged infusion may result in hearing loss and profound electrolyte imbalance

Howlett J. Can J Cardiol 2008

Diuresis - Consequences

- Electrolyte disturbances > Arrhythmias
- Intravascular depletion
- Hypotension
- Renal dysfunction
- Activation of neurohormones and RAA system

ESCAPE Trial
Relation between dose of loop diuretics and outcomes



Hasselblad V. Eur J Heart Failure 2007

Vasodilation

- Addition of a vasodilator to diuretic therapy is most beneficial
- Early (~ 6 hours) initiation is associated with improved outcomes (ADHERE)
- Nitroglycerin and nitroprusside
- No role for Nesiretide

Inotrope Therapy

- Alleviate HF symptoms
- Improvement in hemodynamics
- Serious adverse effects

Inotropic drugs – to be used only in ADHF refractory to diuretics and vasodilators		
Dopamine	1 µg/kg/min to 3 µg/kg/min IV	'Renal' dose
	3 µg/kg/min to 20 µg/kg/min	To support BP and cardiac output
Dobutamine	2 µg/kg/min to 20 µg/kg/min	To support cardiac output
Milrinone	50 µg/kg bolus over 15 min then 0.25 mg/kg/min to 0.75 mg/kg/min infusion	ADHF refractory to diuretics and vasodilators

OPTIME-CHF: Milrinone Vs. Placebo

Primary outcomes and hospitalization

Outcome	Placebo (n = 472)	Milrinone (n = 477)	*P* Value
Days of hospitalization for cardiovascular causes within 60 days			
Median (IQR)*	7 (4, 14)	6 (4, 13)	.71
Mean (SD)	12.5 (14.0)	12.3 (14.1)	
Days of hospitalization from infusion to initial discharge			
Median (IQR)	5 (4, 8)	5 (4, 7)	.99
Mean (SD)	7.0 (6.6)	7.0 (6.2)	
Days of hospitalization for cardiovascular causes from discharge to 60 days			
Median (IQR)	0 (0, 5)	0 (0, 5)	.59
Mean (SD)	5.9 (12.5)	5.7 (12.6)	
Days of hospitalization for any cause within 60 days			
Median (IQR)	8 (4, 16)	7 (4, 15)	.83
Mean (SD)	13.5 (14.4)	13.4 (14.7)	
Death or readmission within 60 days, No./Total (%)	164/464 (35.3)	166/474 (35.0)	.92

*IQR indicates interquartile range.

Cuffe MS. JAMA 2002

OPTIME-CHF: Milrinone Vs. Placebo

Adverse event and mortality

Adverse Event, No. (%)	Placebo (n = 472)	Milrinone (n = 477)	*P* Value
Treatment failure cause at 48 hours	43/466 (9.2)	97/470 (20.6)	<.001
Progression of heart failure	6.8	7.9	.54
Adverse event	2.1	12.6	<.001
Events during index hospitalization			
Myocardial infarction	2 (0.4)	7 (1.5)	.18
New atrial fibrillation or flutter	7 (1.5)	22 (4.6)	.004
Ventricular tachycardia or fibrillation†	7 (1.5)	16 (3.4)	.06
Sustained hypotension‡	15 (3.2)	51 (10.7)	<.001
Death	11 (2.3)	18 (3.8)	.19
Events within 60 days			
Myocardial infarction	5/448 (1.1)	10/462 (2.2)	.21
New atrial fibrillation or flutter	16/446 (3.6)	26/462 (5.6)	.14
Ventricular tachycardia or fibrillation	20/446 (4.5)	23/461 (5.0)	.72
Death	41/463 (8.9)	49/474 (10.3)	.41

*Total number of patients listed only when it varies from number randomized as shown.
†Reported by the investigator.
‡Defined as a systolic blood pressure below 80 mm Hg for more than 30 minutes, requiring intervention.

Cuffe MS. JAMA 2002

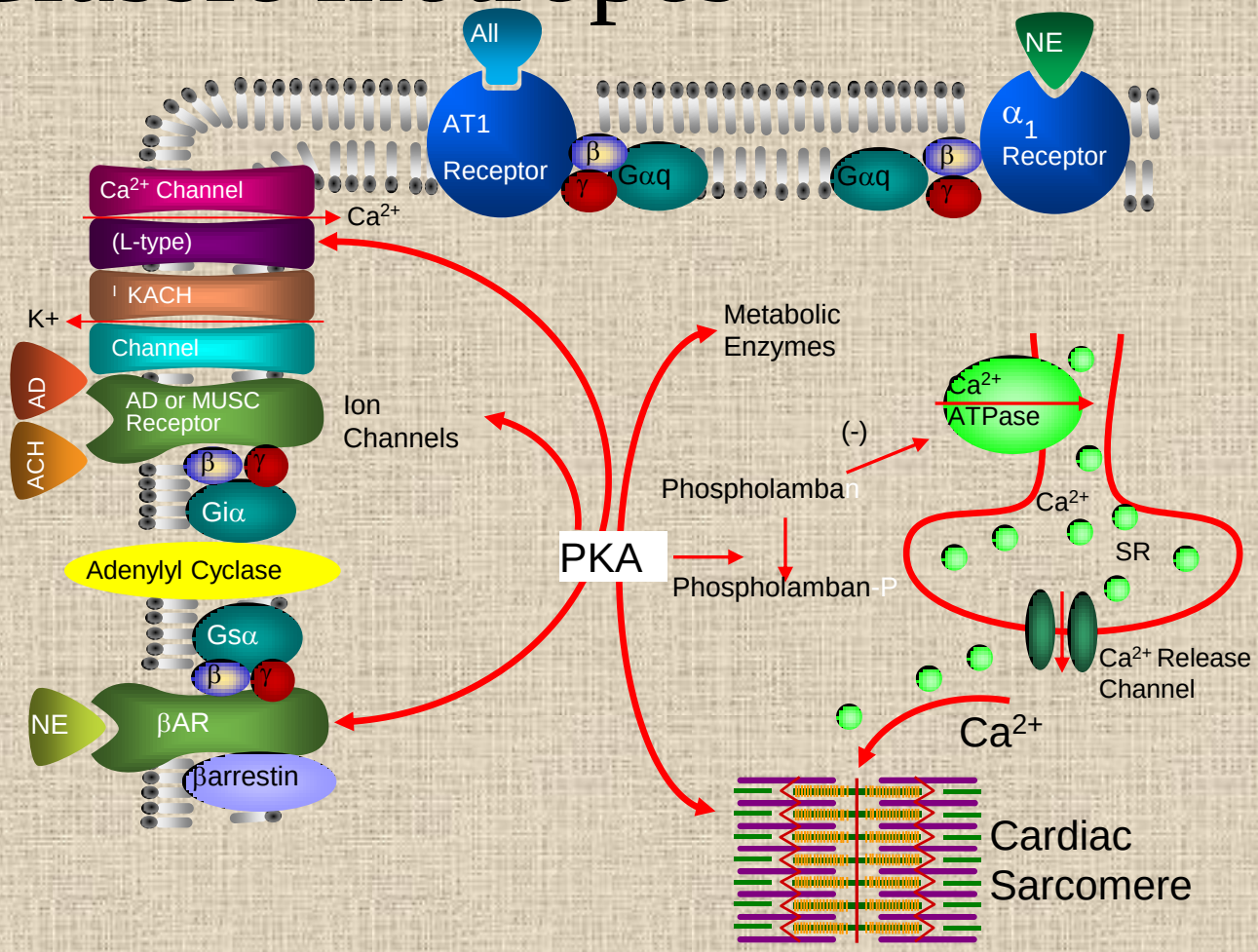
Classic inotropes

Indirect Mechanisms

PKA phosphorylates proteins throughout the myocyte

↓

Intracellular [Ca^{2+}] increases



Classic inotropes

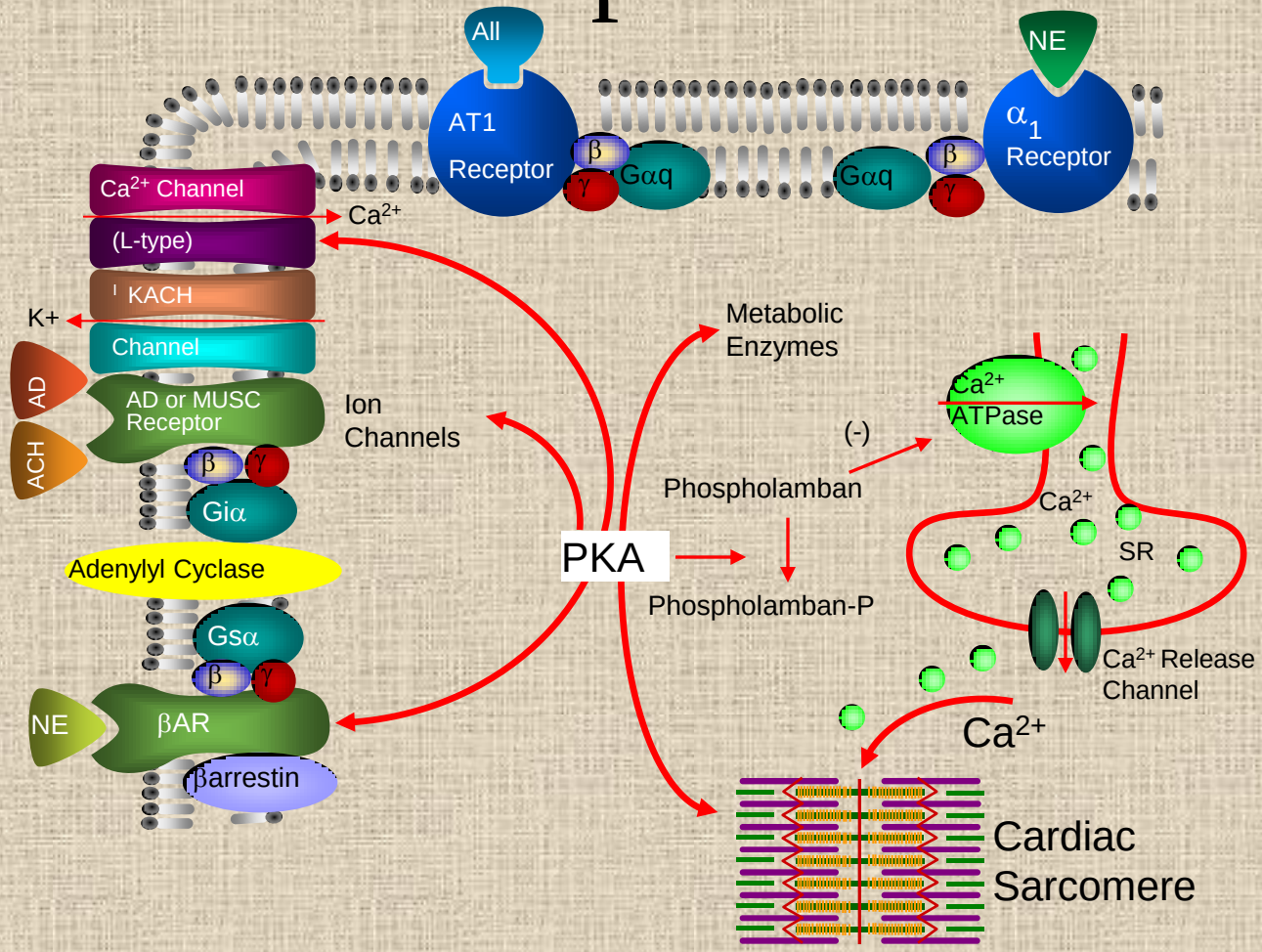
Indirect Mechanisms

PKA phosphorylates proteins throughout the myocyte

↓

Intracellular [Ca^{2+}] increases

- ↑ Contractility
- ↑ Heart rate
- ↓ Blood Pressure
- ↑ O_2 Demand
- ↓ Efficiency
- ↑ Arrhythmias



Targeting the Sarcomere

Therapeutic Hypothesis

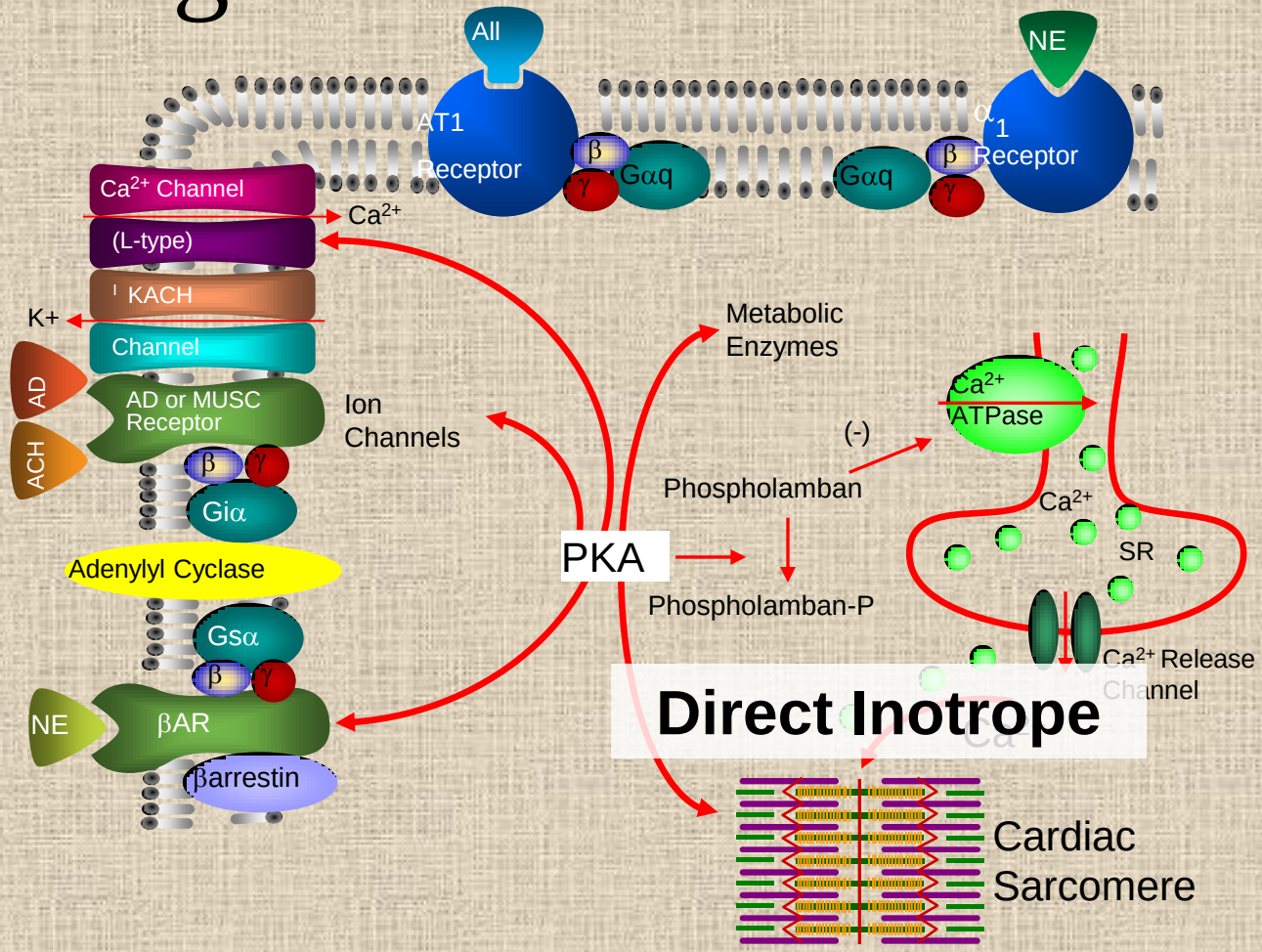
Directly target the sarcomere

Ø PKA activation

↓

Intracellular [Ca^{2+}] unchanged

- ↑ Contractility
- ↔ Heart rate?
- ↔ Blood Pressure?
- ↔ O_2 Demand?
- ↑ Efficiency?
- ↔ Arrhythmias?



Mechanisms of Inotropy

Table I **Inotropic mechanisms and drugs**

Inotropic mechanism	Drugs
Sodium-potassium-ATPase inhibition	Digoxin
β-Adrenoceptor stimulation	Dobutamine, dopamine
Phosphodiesterase inhibition	Enoximone, milrinone
Calcium sensitization	Levosimendan
Sodium-potassium-ATPase inhibition plus SERCA activation	Istaroxime
Acto-myosin cross-bridge activation	Omecamtiv mecarbil
SERCA activation	Gene transfer
SERCA activation plus vasodilation	Nitroxyl donor; CXL-1020
Ryanodine receptor stabilization	Ryanodine receptor stabilizer; S44121
Energetic modulation	Etomoxir, pyruvate

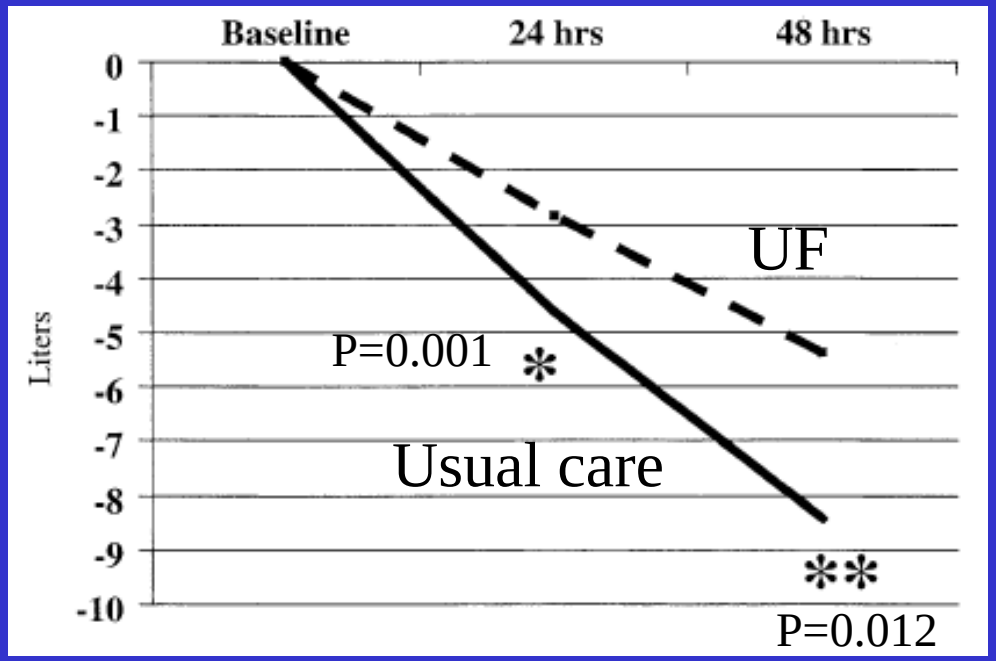
Hassenfuss G, Teerlink JR. *Eur Heart J* 2011

Ultrafiltration

- Advantages
  - Adjustable fluid-removal volume and rates
  - Neutral effect on serum electrolytes
  - Decreased neurohormonal activation

RAPID-CHF: UF Vs. Usual Care

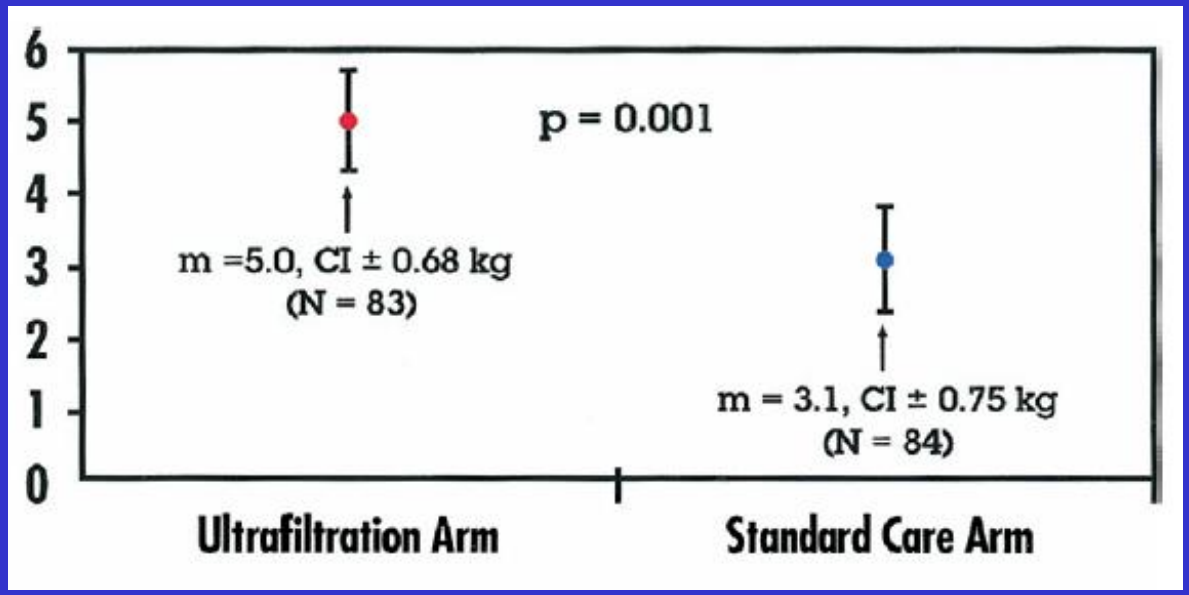
Fluid Removal at 24 and 28 hours



Bart A. JACC 2005

UNLOAD: UF Vs. Usual Care

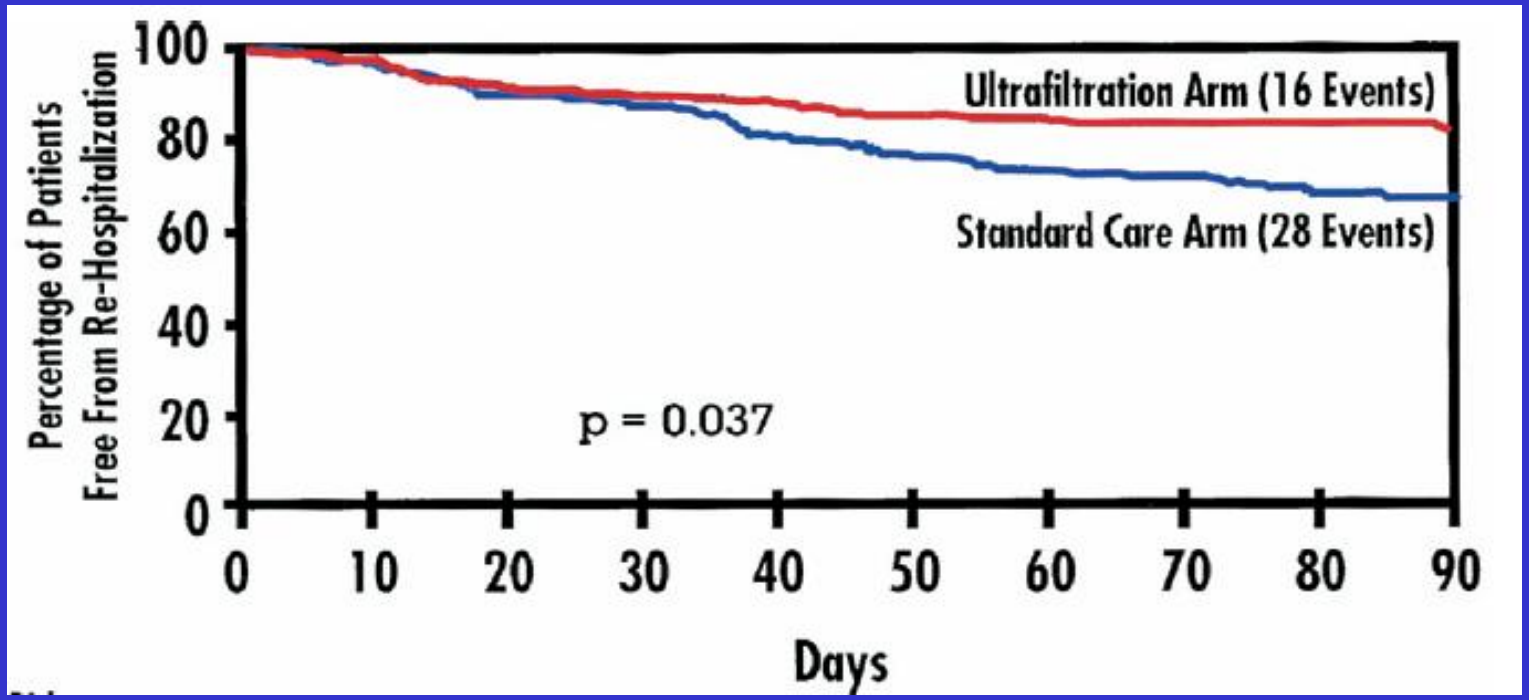
Primary Efficacy End Point: Weight Loss (Kg) at 48 Hrs



Costanzo MR. JACC 2007

UNLOAD: UF Vs. Usual Care

Freedom from Heart Failure Hospitalization



Costanzo MR. JACC 2007

CARRESS-HF Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Givertz, M.D., Christopher M. O'Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Martin M. LeWinter, M.D., Elizabeth O. Ofili, M.D., M.P.H., Lynne W. Stevenson, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Horng H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Anstrom, Ph.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Jenny C. Ibarra, R.N., M.S.N., Alice M. Mascette, M.D., and Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network

Stepped Pharmacologic Care Arm

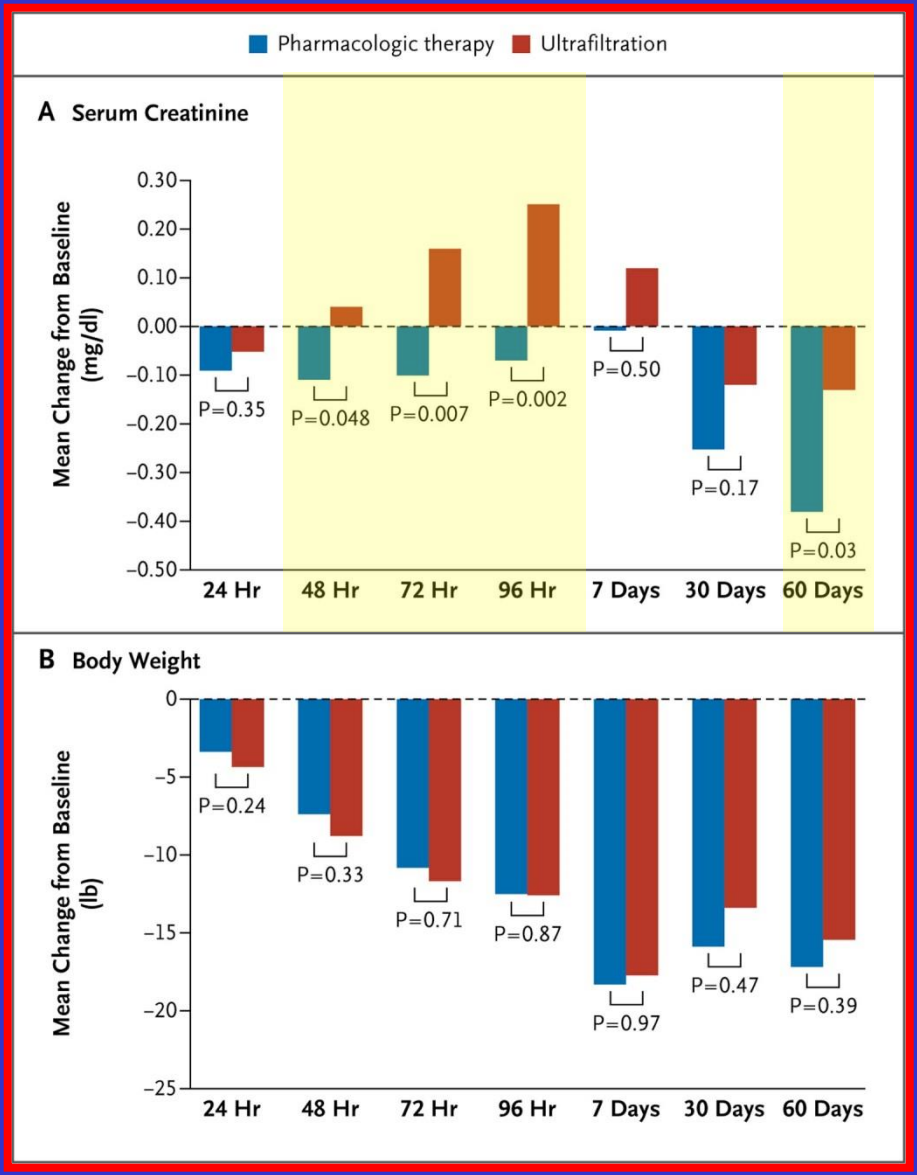
- At randomization and all time points (24, 48, 72, 96 hrs), if:
  - U/o > 5L/d: reduce current diuretic regimen as desired
  - U/o 3-5 L/d: continue current diuretic regimen
  - U/o < 3L/d: advance to next step on table

	Current Dose		Suggested Dose	
	loop (/day)	thiazide	loop (/day)	thiazide
A	≤ 80	+ or -	40 mg iv bolus+ 5 mg/hr	0
B	81-160	+ or -	80 mg iv bolus+ 10 mg/hr	5 mg metazolone QD
C	161-240	+ or -	80 mg iv bolus+ 20 mg/hr	5 mg metazolone BID
D	> 240	+ or -	80 mg iv bolus+ 30 mg/hr	5 mg metazolone BID

Ultrafiltration Arm

- UF initiated at fluid removal rate of 200 cc/h and continued until signs and symptoms of congestion optimized

Changes in Cr and Wt at Various Time Points



Bart BA et al. N Engl J Med 2012;367:2296-2304

Serious Adverse Events

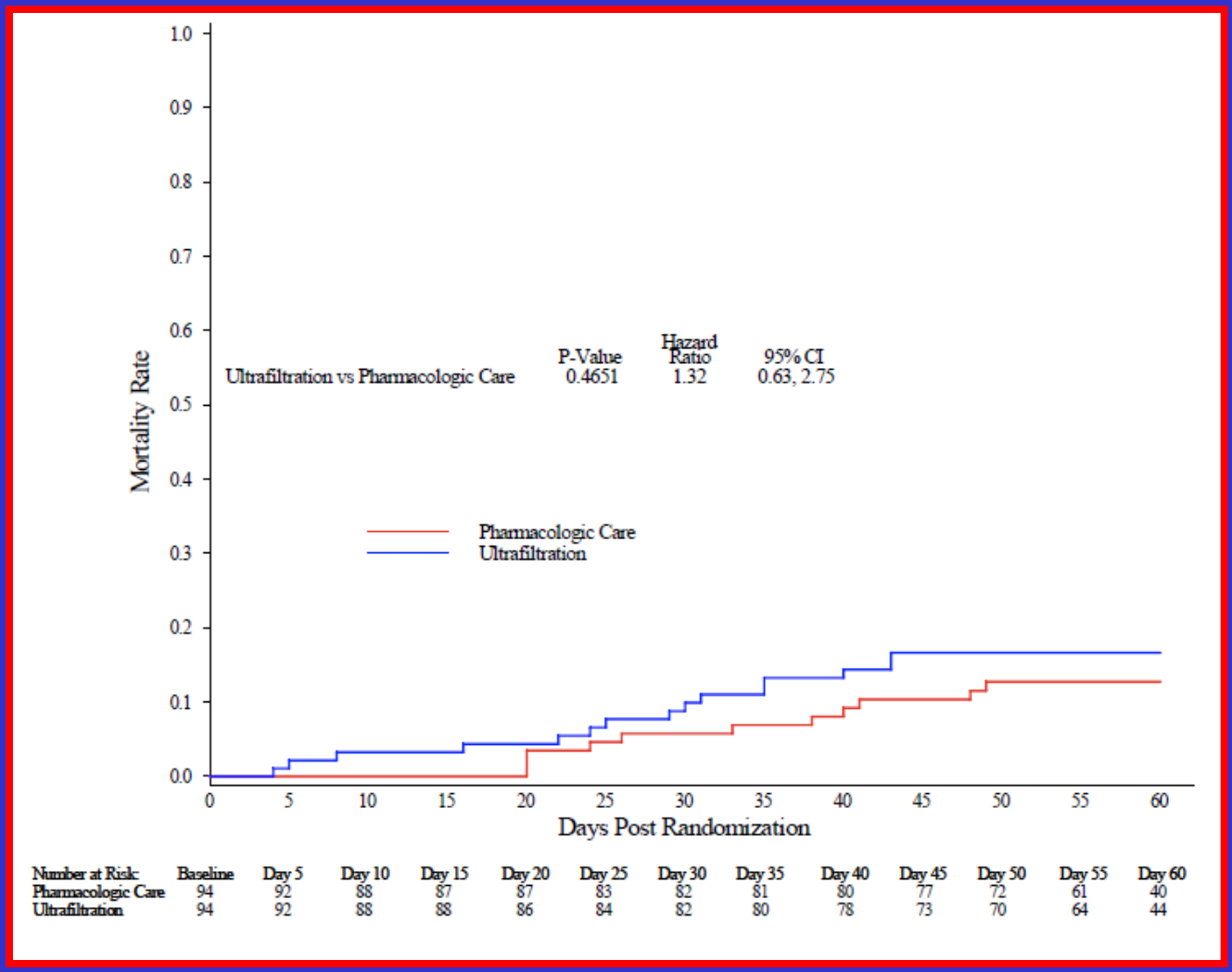
Table 3. Serious Adverse Events.

Event	Pharmacologic Therapy (N=94)	Ultrafiltration (N=94)
	no. of patients (%)	
Any	54 (57)	68 (72)
Heart failure	28 (30)	31 (33)
Other cardiovascular disorder	5 (5)	6 (6)
Renal failure	14 (15)	17 (18)
Anemia or thrombocytopenia	5 (5)	8 (9)
Catheter-site hemorrhage	0	2 (2)
Electrolyte disorder*	3 (3)	0
Gastrointestinal hemorrhage	3 (3)	7 (7)
Pneumonia or other respiratory disorder	6 (6)	10 (11)
Sepsis, bacteremia, or cellulitis	4 (4)	8 (9)
Other	19 (20)	17 (18)

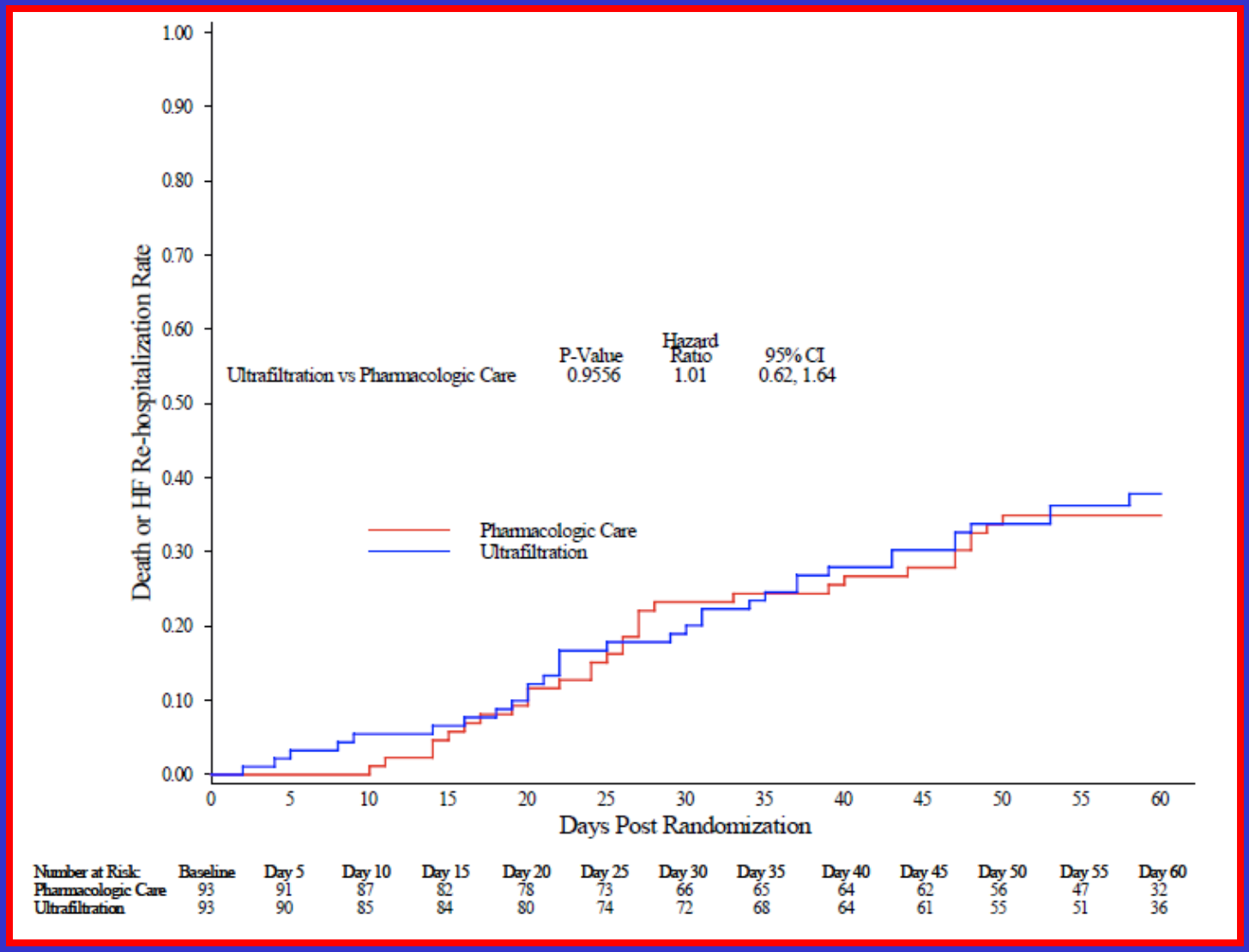
* Included in this category are hyperkalemia, hypokalemia, hypernatremia, hyponatremia, and hyperuricemia.

Bart BA et al. N Engl J Med 2012;367:2296-2304

Kaplan-Meier Time to Death



Kaplan-Meier Time to Death or HF Rehospitalization

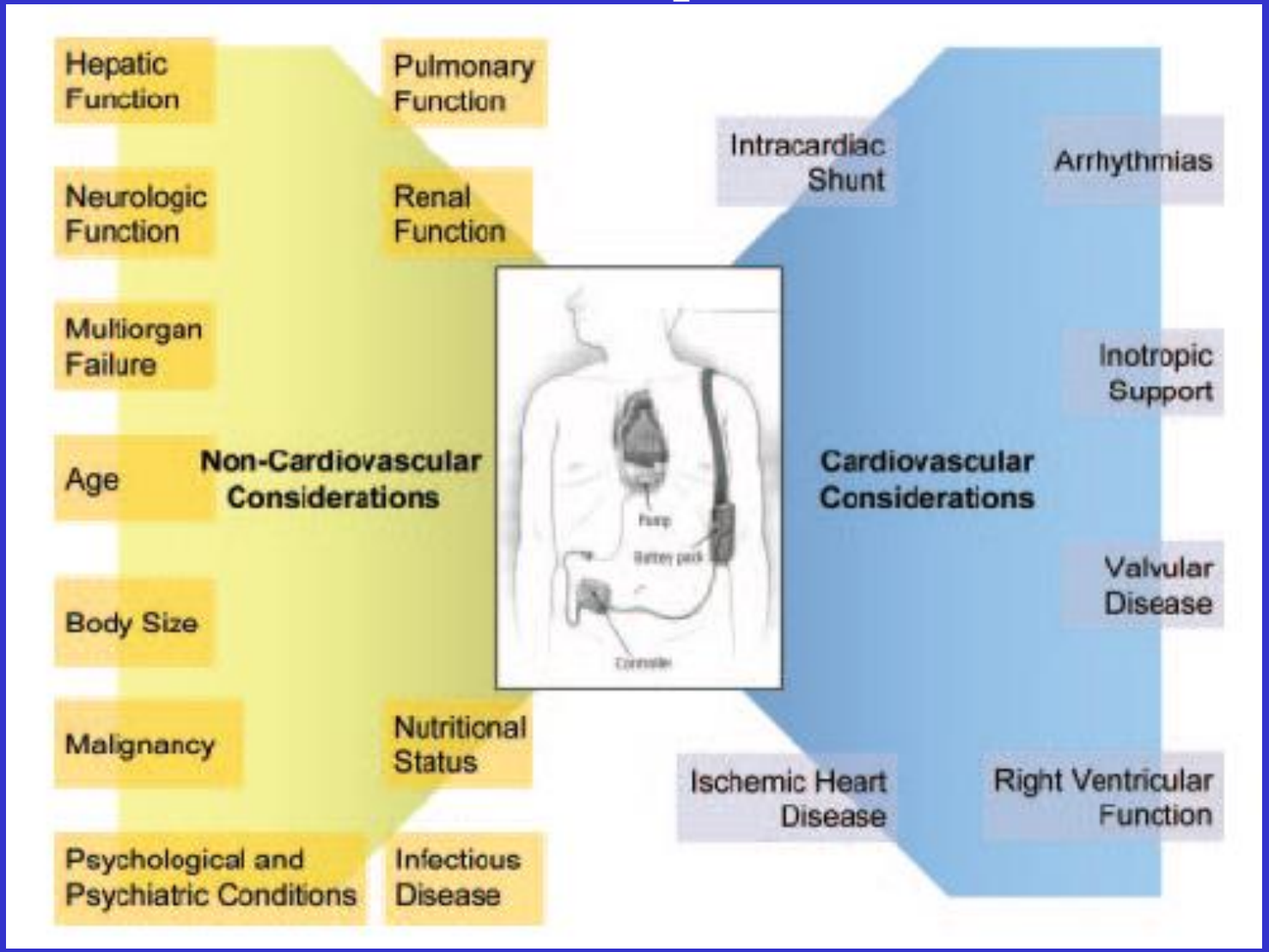


Conclusions

- Use of a stepped pharmacologic-therapy algorithm was superior to a strategy of UF for the preservation of renal function at 96 hours, with a similar amount of wt loss
- UF was associated with a higher rate of adverse events

	Heartware	Heart-mate II	Impella	Centrimag	ECMO
	Durable MCS		**Short Term MCS**		
Mechanism	Centrifugal flow	Axial flow	Axial flow	Centrifugal	Centrifugal pump in circuit
Long-term support	Yes	Yes	7 days	30 days	7 days
RV support	No	No	Yes	Yes	Yes
Indications	BTT BTC DT	BTT BTC DT	Bridge to recovery, Acute LV failure	Bridge to recovery, Post-op shock	Acute Biv failure, poor oxygenation

Factors involved in determining appropriateness of VAD implantation



LVAD RISK SCORES

Patient name: _____
MRN: _____
Date of Assessment: _____

The Columbia (Rao) Risk Score

Rao V, Oz M et al. J Thorac Cariovasc Surg 2003; 125: 855-62

- Retrospective review 130 patients pulsatile HeartMate XVE LVAD (1996-2001).

Variable	Score Weighting	Current Patient	Total for this patient:
Intubated/Ventilated?	4		
Post-Cardiotomy Shock	2		
Previous LVAD	2		
CVP > 16	1		_____
PT > 16s	1		

- Score Interpretation: Scores > 5 = high risk with operative risk mortality 46%
  Scores ≤ 5 = low risk with operative mortality 12%

The Lietz-Miller Score

Lietz K et al. Circulation 2007; 116; 497-505

- Retrospective review 280 Destination Therapy pulsatile HeartMate XVE LVAD (2001-2005). Older VADs, 72.9% pump failure in 2 yrs .

Variable	Score Weighting	Current Patient	Total for this patient:
Platelet Count ≤ 148	7		
Serum Albumin ≤ 33 g/L	5		
INR > 1.1	4		
Vasodilator therapy (Intravenous)	4		
Mean PAP ≤ 25 mm Hg	3		_____
AST > 45 u/ml	2		
Hematocrit ≤ 34%	2		
Blood Urea Nitrogen > 18.2 mmol/L	2		
No intravenous inotropes	2		

- Score Interpretation:

Risk Category	Risk Score	In-Hospital Mortality within 90 days	Survival to Hospital Discharge	1 Yr Survival
Low	0 - 8	2% (1-3)	87.5%	81.2%
Medium	9 – 16	12% (8-19)	70.5%	62.4%
High	17 – 19	44% (33-56)	26%	27.8%
Very High	>19	81% (66-91)	13.7%	10.7%

Right Ventricular Failure Risk Score

Matthews et al. J Am Coll Cardiol 2008; 51:2163-72

- Retrospective review 197 patients mostly 1st generation VADs (1996 – 2006). RV failure defined by post-op need for inotropes >14 days, iNO > 48hrs , RV mechanical support.

Variable	Score Weighting	Current Patient	Total for this patient:
Vasopressor Requirement	4		
AST > 80 U/L	2		
Bilirubin > 34.2 umol/L	2.5		_____
Creatinine > 203 umol/L	3		

- Score Interpretation:

RVFRS	Odds Ratio of RVF	180 day survival
< 3.0	0.49	90% ± 3
4 - 5	2.8	80% ± 8
> 5.5	7.6	66% ± 9

Case Presentation

- Discussion
  - Multiple comorbidities
  - Not a heart transplant candidate
    - Pulmonary hypertension
  - High risk for VAD
    - Two previous surgeries
      - RV attached to sternunm
      - Poor RV function

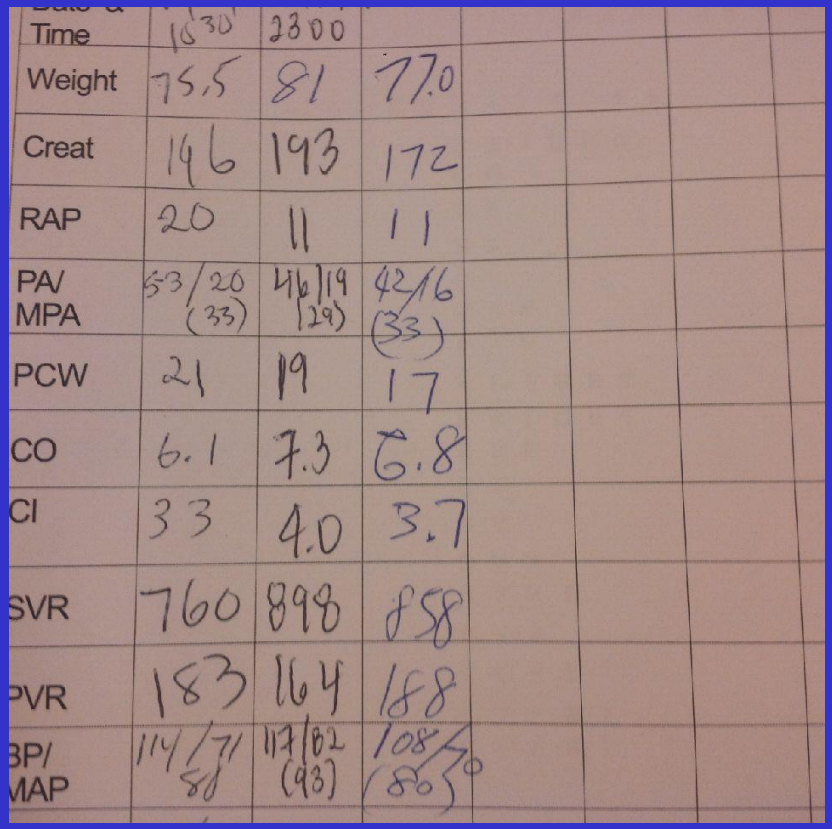
Case Presentation

- Plan

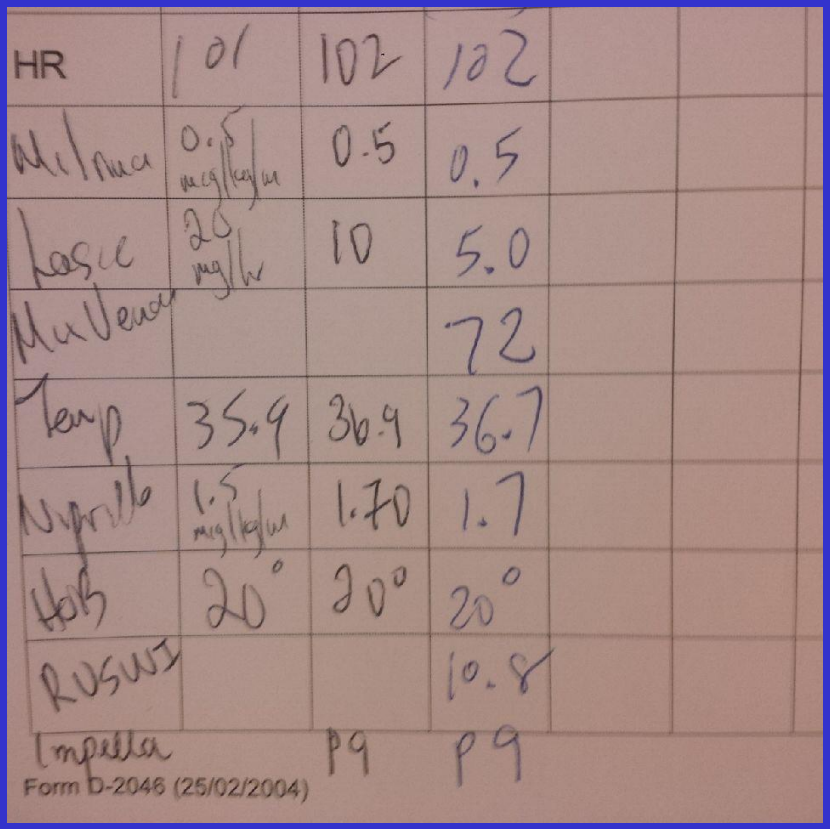
  - Optimization of RV
  - IMPELLA 5.0 and UF

Case Presentation

- Hemodynamics



Time	1830	2300	
Weight	75.5	81	77.0
Creat	146	193	172
RAP	20	11	11
PA/ MPA	53/20 (33)	46/19 (29)	42/16 (33)
PCW	21	19	17
CO	6.1	7.3	6.8
CI	33	4.0	3.7
SVR	760	898	858
PVR	183	164	188
BP/ MAP	114/71 88	117/82 (93)	108/ (80)



HR	101	102	102
Milrinone	0.5 mcg/kg/m	0.5	0.5
Lasix	20 mg/hr	10	5.0
MixVenous			72
Temp	35.9	36.9	36.7
Nipride	1.5 mcg/kg/m	1.70	1.7
HOB	20°	20°	20°
RUSVI			10.8
Impella		P9	P9

Form D-2046 (25/02/2004)

Summary

Management of AHF is not unchanged

Core drug and device therapeutics approaches remain largely unchanged

Goal of treatment

- Establish patient's risk
- Stabilize and relieve symptoms
- Initiate therapy to improve long-term survival and prevent re-hospitalization