Treatment of ADHF:

New Therapeutics and Practical Problems

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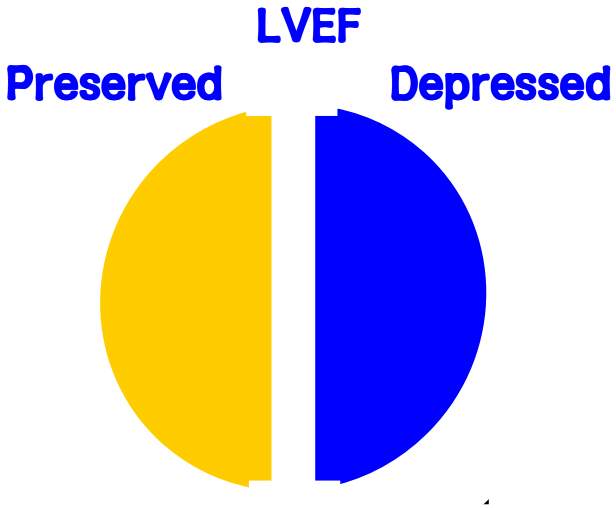
Acute Decompensated HF(ADHF)

- ADHF is a hemodynamic disorder associated with fluid retention and peripheral vasoconstriction.
- Worsening hemodynamic congestion leads to clinical congestion, primary cause of hospitalization
- Episode of worsening congestion result in poor clinical outcome and high coast for care.

Most Patients: Volume Overloarded

("Wet" or Hypervolemic)

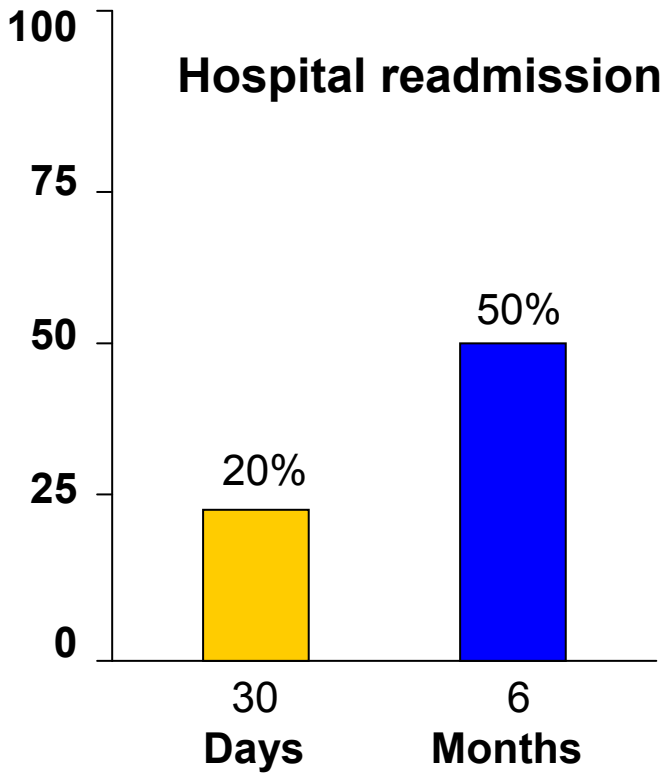
- Dyspnea 89%
- Pulmonary congestion(CXR) 74%
- Peripheral edema 65%
- Dyspnea at rest 34%

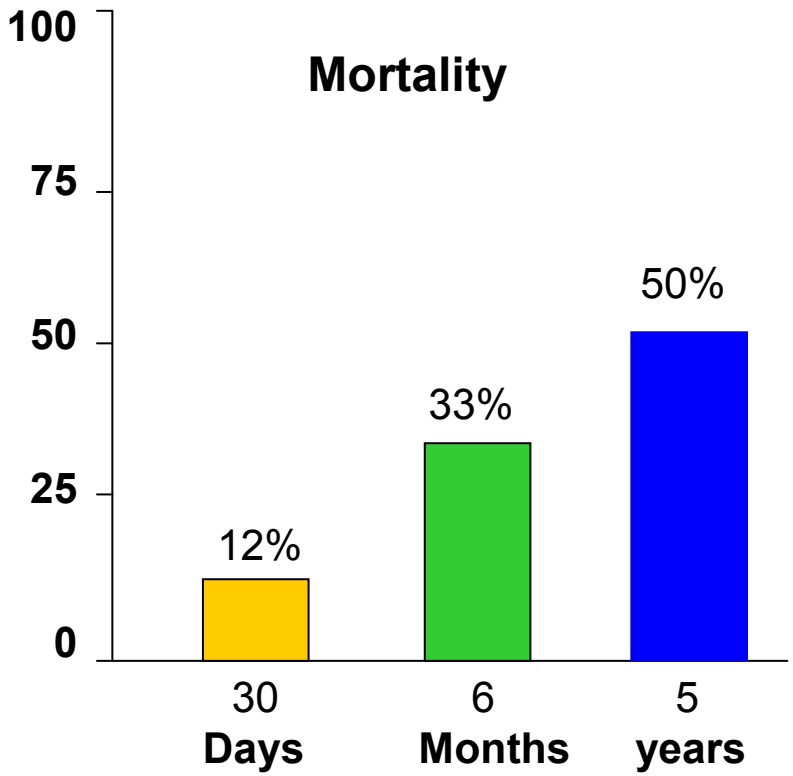


Average systolic BP: 140mmHg

by ADHERE registry

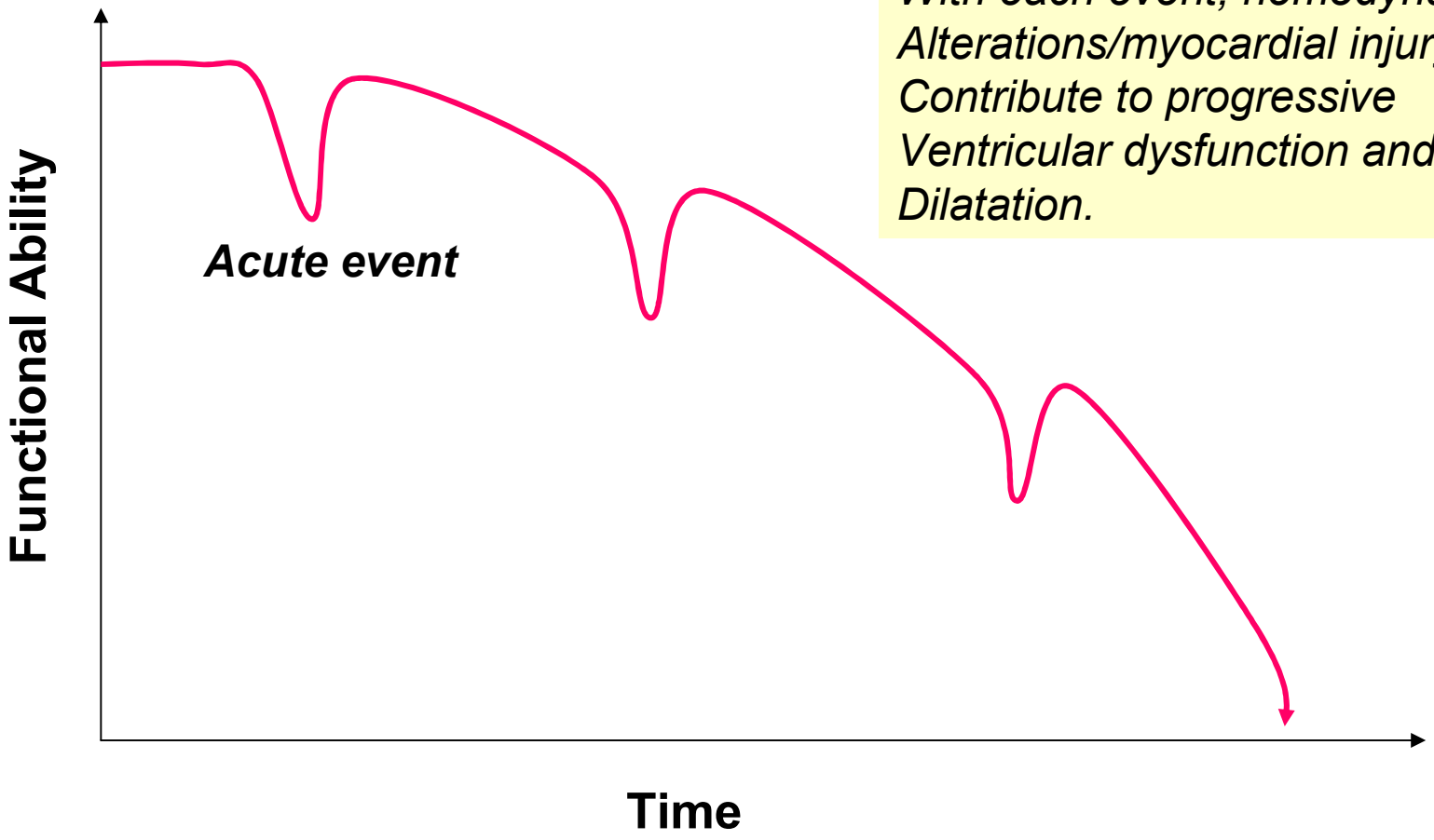
Outcomes in Hospitalized ADHF





Median LOS 6 days
N=38,702
Rev Cardiovasc Med 2002:3;53
Arch Intern Med 2002:162;1689

Acute Exacerbations Contribute to the Progression



With each event, hemodynamic Alterations/myocardial injury Contribute to progressive Ventricular dysfunction and Dilatation.

Jain et al. Am Heart J. 2003:145;S3-S17

Goals of ADHF Therapy

- Alleviate symptoms
- Reduce extracellular fluid volume excess (“congestion”)
- Improve hemodynamics
  - Decrease RV and LV filling pressure
  - Increase CO
- Maintain perfusion to vital organ

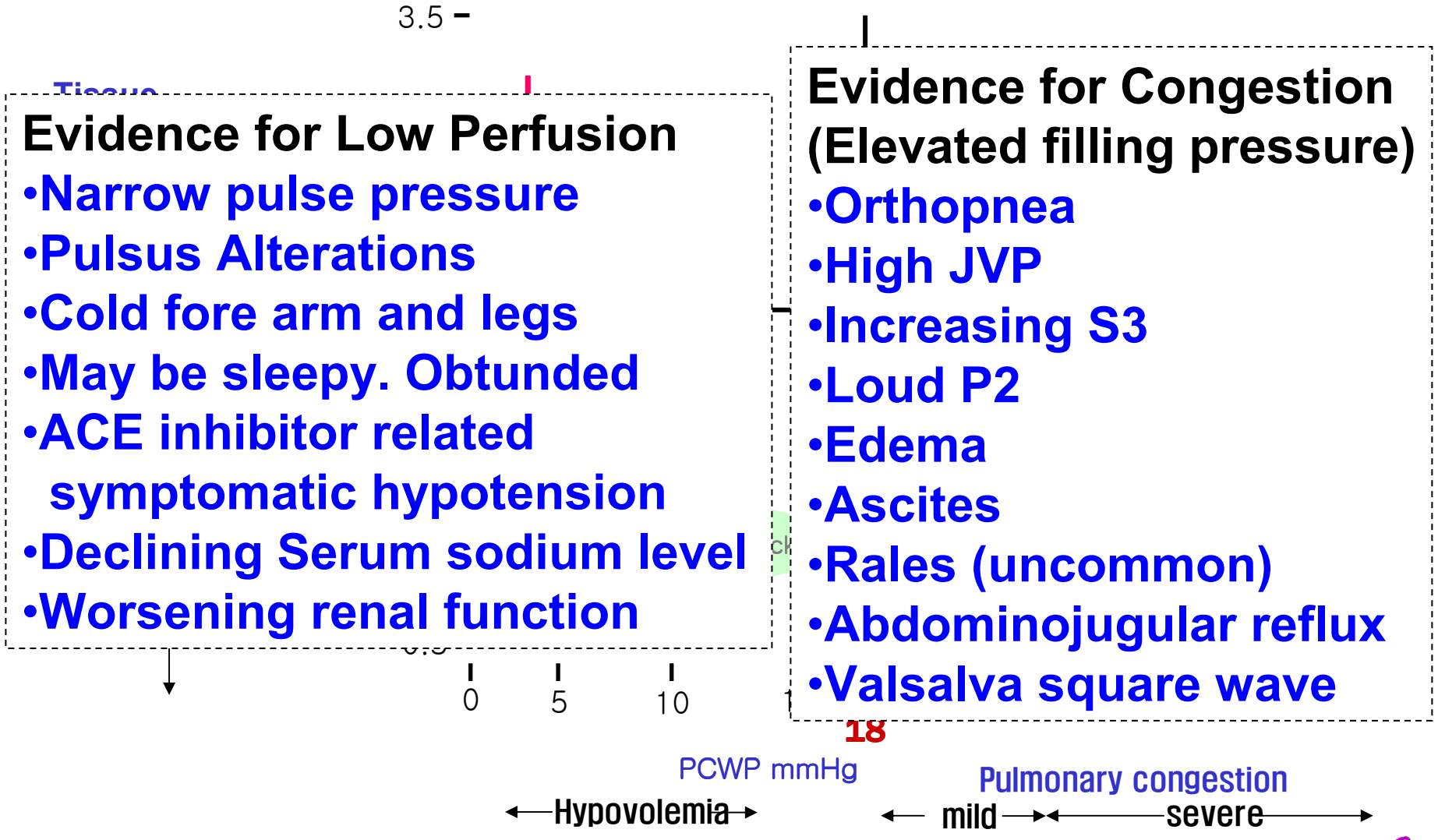
How to Accomplish These Goals?

- **With hemodynamic interventions**
  - **Pharmacological approach**
  - **Mechanical intervention**

Pharmacological Approach

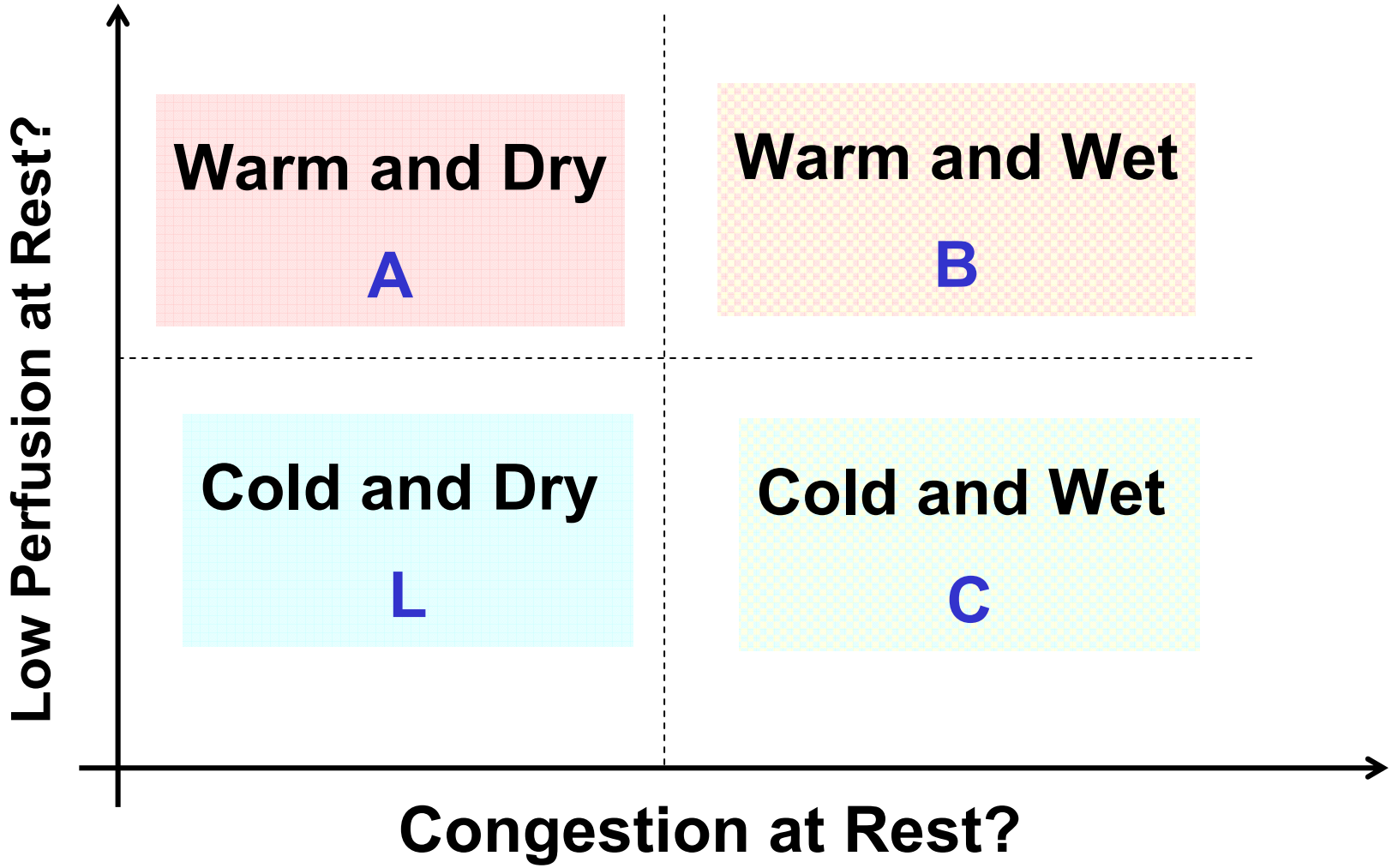
1. Diuretics to reduce ECF volume
   - IV loop diuretics±metolazone/thiazide
   - Ultrafiltration
2. IV vasodilator to reduce LV or RV filling pressure
   - Nesiritide, nitroglycerin, nitroprusside
3. IV inotropic agents to improve CO
   - Sympathomimetic agents
   - Phosphodiesterase inhibitors
   - Calcium sensitizer, (myosin sensitizers)

Forrester Classification



Forrester et al. Am J Cardiol 1977;39:137

Two minute Assessment of Hemodynamic Status



Hemodynamic Profiles and Outcomes

Patient Profile	N(%)	6-M Mortality
Dry and Warm	27.2%	11%
Wet and Warm	49.1%	22%
Wet and Cold	20.1%	40%
Dry and Cold	3.5%	15%

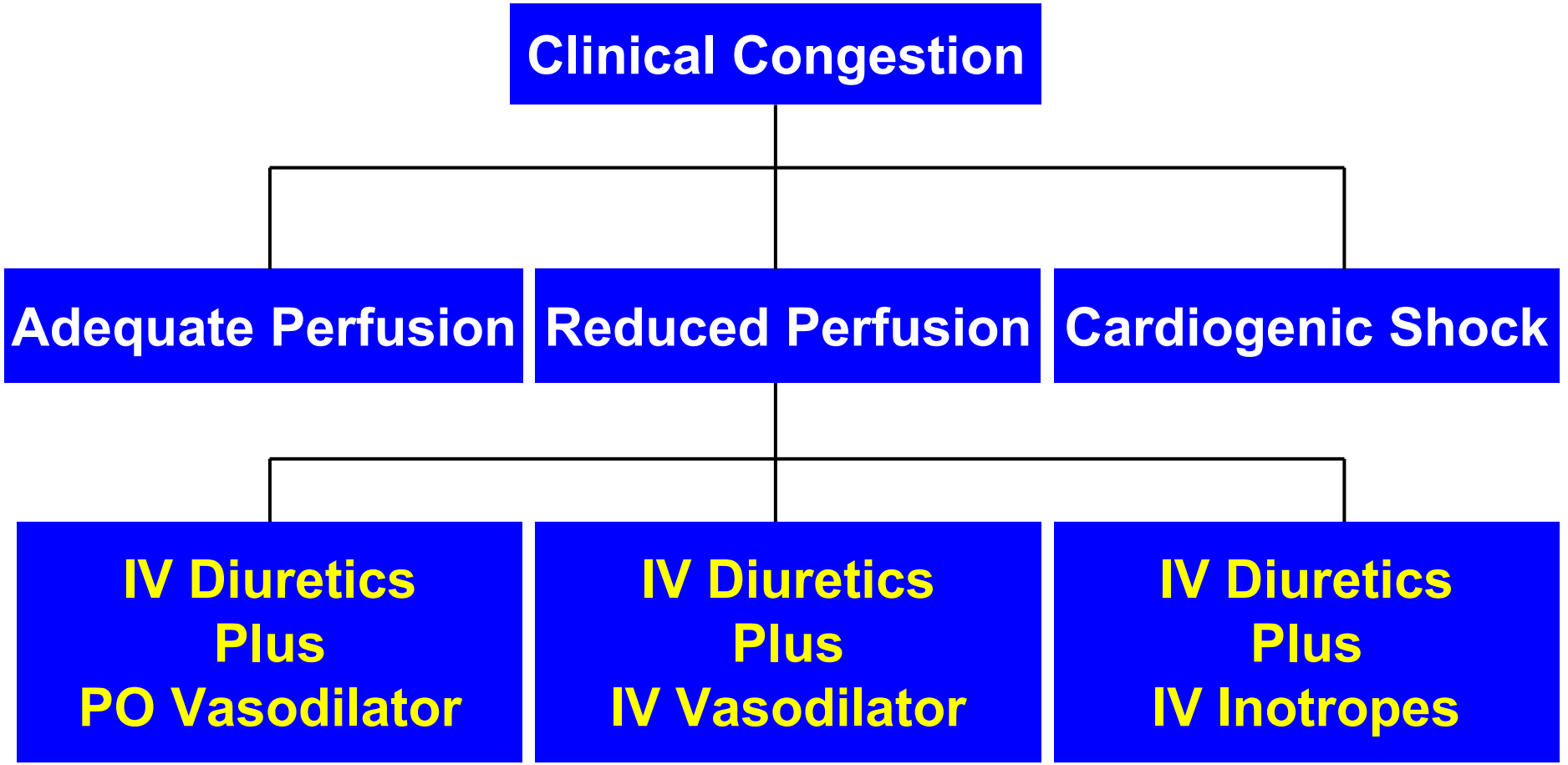
Norria A. et. Al. JACC 2003;41:1707-1804

Accuracy of PE for Estimating Hemodynamics

Variable	Sensitivity(%)	Specificity(%)	PPA(%)	NPA(%)
RAP				
JVP	48	78	60	69
Edema	10	94	55	60
Cardiac Index				
Pulse Pres	27	69	52	44
PCW				
S3	36	81	69	54
Dyspnea	50	73	67	57
Rales	13	90	60	48

386 patients with HF undergoing exam. And catheterization
European J of Heart Failure 2005;7:624-630

Approach to Therapy in ADHF



General therapeutic approach in AHF

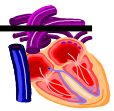
by findings on invasive hemodynamic monitoring

Hemodynamic Characteristic	Suggested therapeutic approach				
CI	Decreased	Decreased	Decreased	Decreased	Maintained
PCWP	Low	Normal	High	High	High
SBP mmHg		>85	<85	>85	
Outline of therapy	Fluid loading	Vasodilator Fluid loading may become necessary	Inotropic agents IV diuretics	Vasodilator IV diuretics Inotrope	IV diuretics Inotropes vasoconstrictive if SBP is low,

Diuretics

Diuretic dosing and administration

Severity	diuretic	Dose (mg)	Comments
Moderate	**Furosemide, or**	20-40	Oral or intravenous according to clinical symptoms
	Bumetanide, or	0.5-1.0	Titrate dose according to clinical response
	Torasemide	10-20	Monitor Na^+, K^+, creatinine and blood pressure
Severe	**Furosemide, or**	40-100	Intravenously
	Furosemide infusion	5-40 mg/h	Better than very high bolus doses
Refractory to loop diuretics	**Bumetanide, or**	1-4	Orally or intravenously
	Torasemid	20-100	Orally
	Add HCTZ, or	25-50 twice daily	Combination with loop diuretic better than very high dose of loop diuretics alone
	Metolazone, or	2.5-10 once daily	Metolazone more potent if creatinine clearance <30 mL/min
	Spironolactone	25-50 once daily	Spironolactone best choice if patient not in renal failure and normal or low serum K^+
In case of alkalosis	**Acetazolamide**	0.5	intravenously
Refractory to loop diuretic and thiazides	**Add dopamine for renal vasodilatation, or dobutamine as an inotropic agent**		Consider ultrafiltration or haemodilalysis if co-existing renal failure

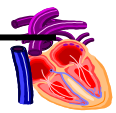


Causes diuretic resistance

1. Intravascular volume depletion
2. Neurohormonal activation
3. Rebound Na^+ uptake after volume loss
4. Hypertrophy of distal nephron
5. Reduced renal perfusion (low output)
6. Impaired gut absorption of an oral diuretic
7. Non-compliance with drugs or diet (high sodium intake)

Managing resistance to diuretics

1. Restrict Na^+/H_2O intake and follow electrolytes
2. Volume repletion in cases of hypovolemia
3. Increase dose and/or frequency of administration of diuretic
4. Use IV administration: oral << IV bolus << IV infusion
5. Combine diuretic therapy
   - Furosemide + HCTZ
   - Furosemide + Spironolactone
   - Metolazone + Furosemide
6. Combine diuretic therapy with dopamine, or dobutamine
7. Reduce the dose of ACEi or use very low doses of ACEi
8. Consider ultrafiltration or dialysis if response to above strategies ineffective



Hyponatremia

- Prevalence of 10% in HF, especially in acute or end stage HF.
- Increase as a function of fundamental disease.
- Powerful predictor of mortality and morbidity

- Baroreceptor stimulation in carotid body, LV and ascending aorta.
- Water retention by inappropriate AVP
- Solute losses from diuretics Tx.

Vasopressin

arginine vasopressin (AVP)
antidiuretic hormone (ADH)

Chemistry: Phe - Tyr - Cys *(Nonapeptide)*

Glu - Asn - Cys - Pro - Arg - Gly - NH_2

Clinical preparations:

synthetic arginine vasopressin (human form)
desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP),
synthetic analog with longer duration of action and selective activity for renal effects (Tolvaptan, Lixivaptan, SR-121463, Conivaptan)

AVP: Mechanism of action

- **Three specific G-protein -coupled receptors:**

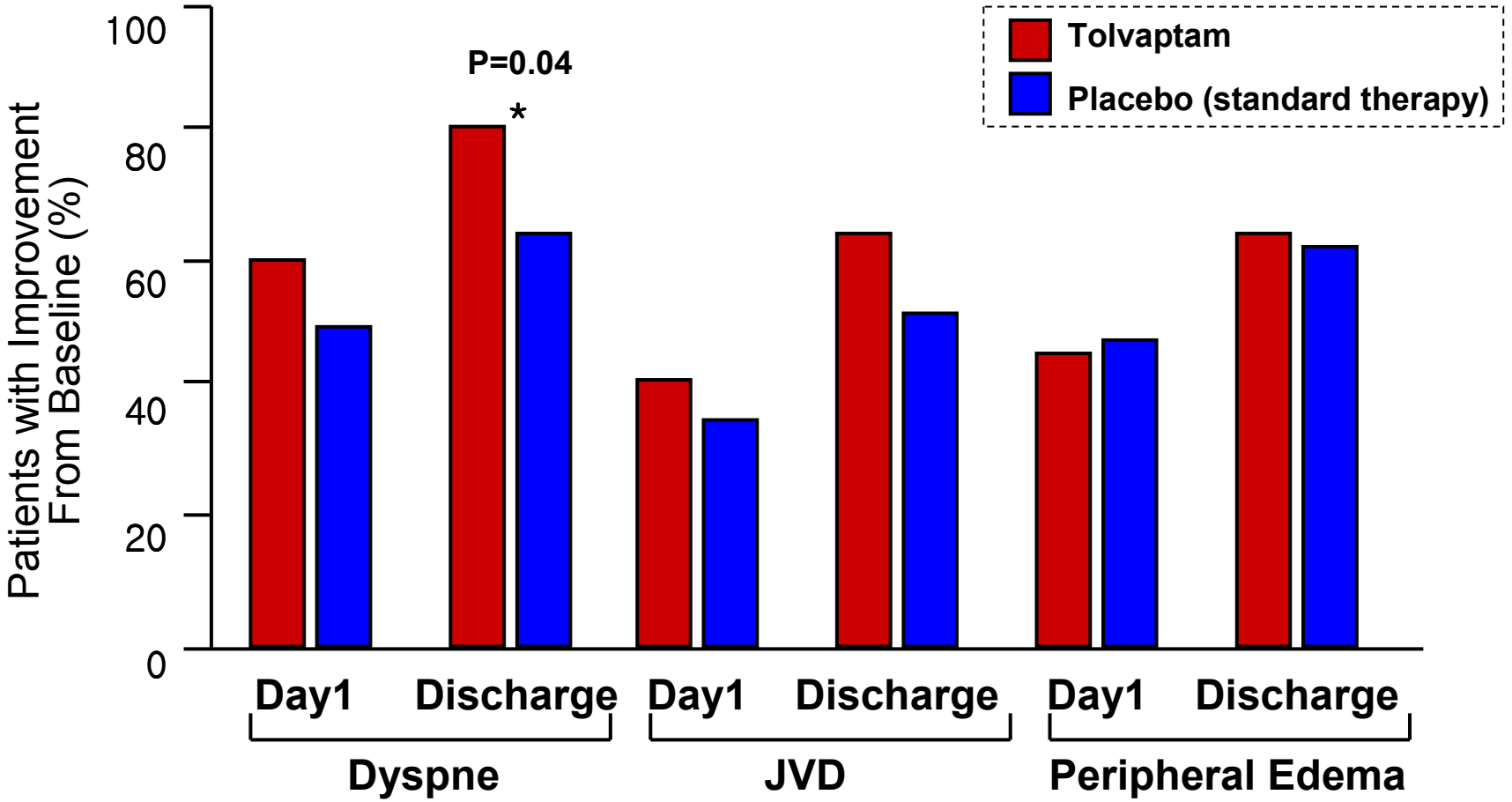
V_{1a} binding	V_{1b} binding	V_2 binding
⇓ ⊕	⇓ ⊕	⇓ ⊕
phospholipase C	phospholipase C	adenylate cyclase
⇓ ⊕	⇓ ⊕	⇓ ⊕
IP_3, Ca^{2+}	IP_3, Ca^{2+}	cAMP
⇓ ⊕	⇓ ⊕	⇓ ⊕
contraction of vascular and GI smooth muscle	potentiation of ACTH secretion by anterior pituitary	**insertion of aquaporin into luminal membrane of renal medullary collecting ducts**

AVP Receptor Antagonists in RCT

	Tolvaptan	Lixivaptan	SR-121463	Conivaptan
Receptor	V_2	V_2	V_2	V_{1a}/V_2
Route of administration	Oral	Oral	Oral/IV	IV
Urine volume	↑	↑	↑	↑
Urine osmo	↓	↓	↓	↓
Serum Na	↑	↑	↑	↑

Effect of Tonlvaptan in ADHF

ACTIVE



Gheorghiade et al. JAMA. 2004;291:1963-1971

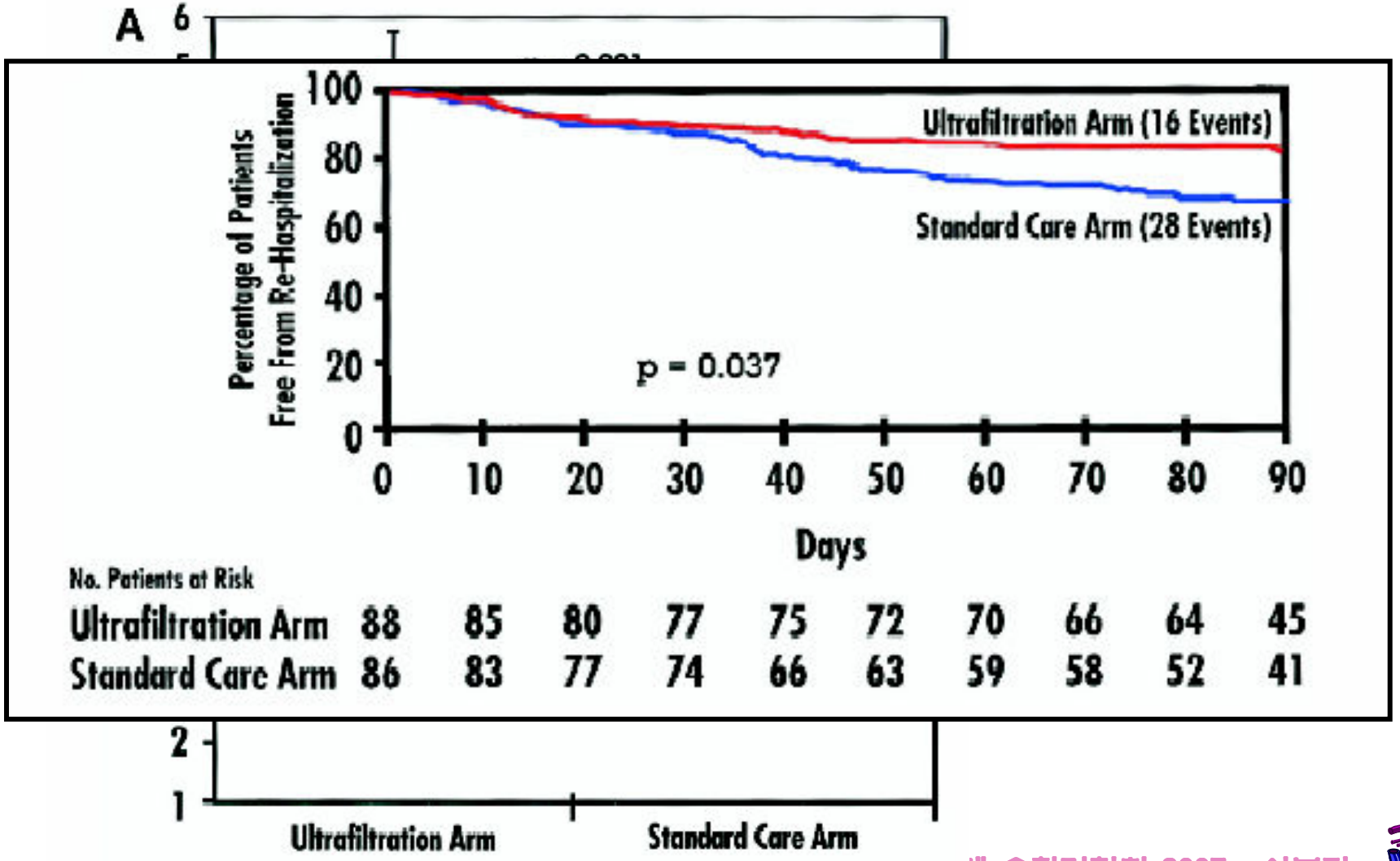
Renal Dysfunction in ADHF

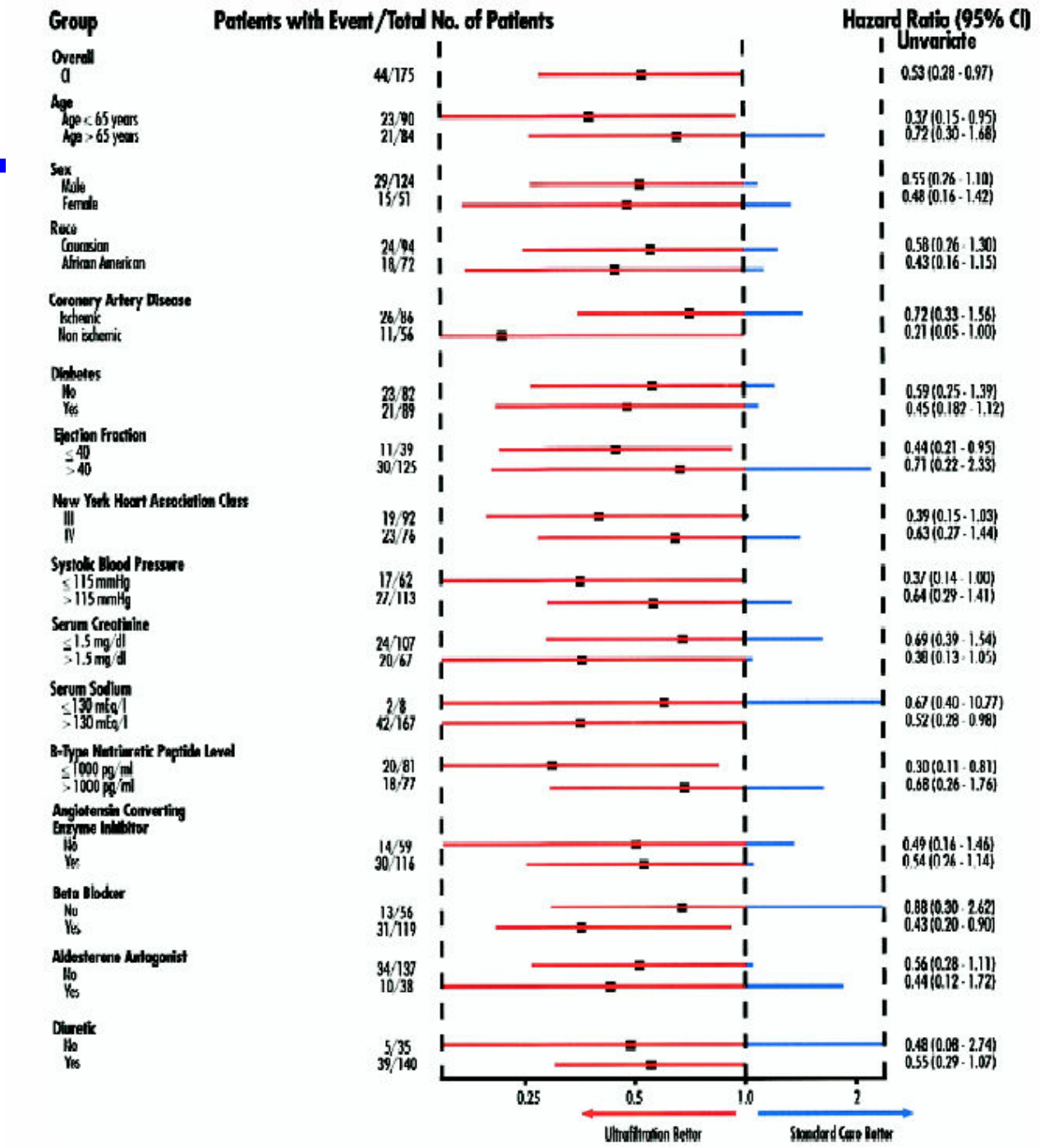
- Common
- Associated with poor prognosis
- WRF may reduced by a less aggressive use of diuretics
  - Small and frequent use
  - Continuous infusion
  - Inotropes, Nesiritide
  - ultrafiltration

Ultrafiltration and ADHF

- Fluid removal 2,800-4,500ml/24h
  (weight loss 2.5-1.9Kg)
- SBP change: -7.7mmHg/24h
- Scr increase 1.0mg/dl

UNLOAD trial




Group
Patients with Event /Total No. of Patients
Hazard Ratio (95% CI)
Unvariate
Overall
CI 44/175 0.53 (0.28 - 0.97)
Age
Age < 65 years 23/90 0.37 (0.15 - 0.95)
Age > 65 years 21/84 0.72 (0.30 - 1.68)
Sex
Male 29/124 0.55 (0.26 - 1.10)
Female 15/51 0.48 (0.16 - 1.42)
Race
Caucasian 24/94 0.58 (0.26 - 1.30)
African American 18/72 0.43 (0.16 - 1.15)
Coronary Artery Disease
Ischemic 26/86 0.72 (0.33 - 1.56)
Non Ischemic 11/56 0.21 (0.05 - 1.00)
Diabetes
No 23/82 0.59 (0.25 - 1.39)
Yes 21/89 0.45 (0.182 - 1.12)
Ejection Fraction
≤ 40 11/39 0.44 (0.21 - 0.95)
> 40 30/125 0.71 (0.22 - 2.33)
New York Heart Association Class
III 19/92 0.39 (0.15 - 1.03)
IV 23/76 0.63 (0.27 - 1.44)
Systolic Blood Pressure
≤ 115 mmHg 17/62 0.37 (0.14 - 1.00)
> 115 mmHg 27/113 0.64 (0.29 - 1.41)
Serum Creatinine
≤ 1.5 mg/dl 24/107 0.69 (0.39 - 1.54)
> 1.5 mg/dl 20/67 0.38 (0.13 - 1.05)
Serum Sodium
≤ 130 mEq/l 2/8 0.67 (0.40 - 10.77)
> 130 mEq/l 42/167 0.52 (0.28 - 0.98)
B-Type Natriuretic Peptide Level
≤ 1000 pg/ml 20/81 0.30 (0.11 - 0.81)
> 1000 pg/ml 18/77 0.68 (0.26 - 1.76)
Angiotensin Converting Enzyme Inhibitor
No 14/59 0.49 (0.16 - 1.46)
Yes 30/116 0.54 (0.26 - 1.14)
Beta Blocker
No 13/56 0.88 (0.30 - 2.62)
Yes 31/119 0.43 (0.20 - 0.90)
Aldosterone Antagonist
No 34/137 0.56 (0.28 - 1.11)
Yes 10/38 0.44 (0.12 - 1.72)
Diuretic
No 5/35 0.48 (0.08 - 2.74)
Yes 39/140 0.55 (0.29 - 1.07)
0.25
0.5
1.0
2
Ultrafiltration Better
Standard Care Better

Vasodilators

Indications and dosing of vasodilators in AHF

Vasodilator	Indication	Dosing	Main side effects	Other
Glyceryl trinitrate, 5-monontrate	Acute heart failure, when blood pressure is adequate	Start 20 ㎍/min, increase to 200 ㎍/min	Hypotension, Headache	Tolerance on continuous use
Isosorvide dinitrate	Acute heart failure, when blood pressure is adequate	Start with 1 mg/h, increase to 10 mg/h	Hypotension, Headache	Tolerance on continuous use
Nitroprusside	Hypertensive risis, cardiogenic shock combined with intoropes	0.3-5 ㎍/kg/min	Hypotension, Isocyanate toxicity	Drug is light sensitive
Nesiritide[a]	Acute decompensated heart failure	Blous 2 ㎍/kg + infusion 0.015-0.03 ㎍ /kg/min	hypotension	

Nitrate

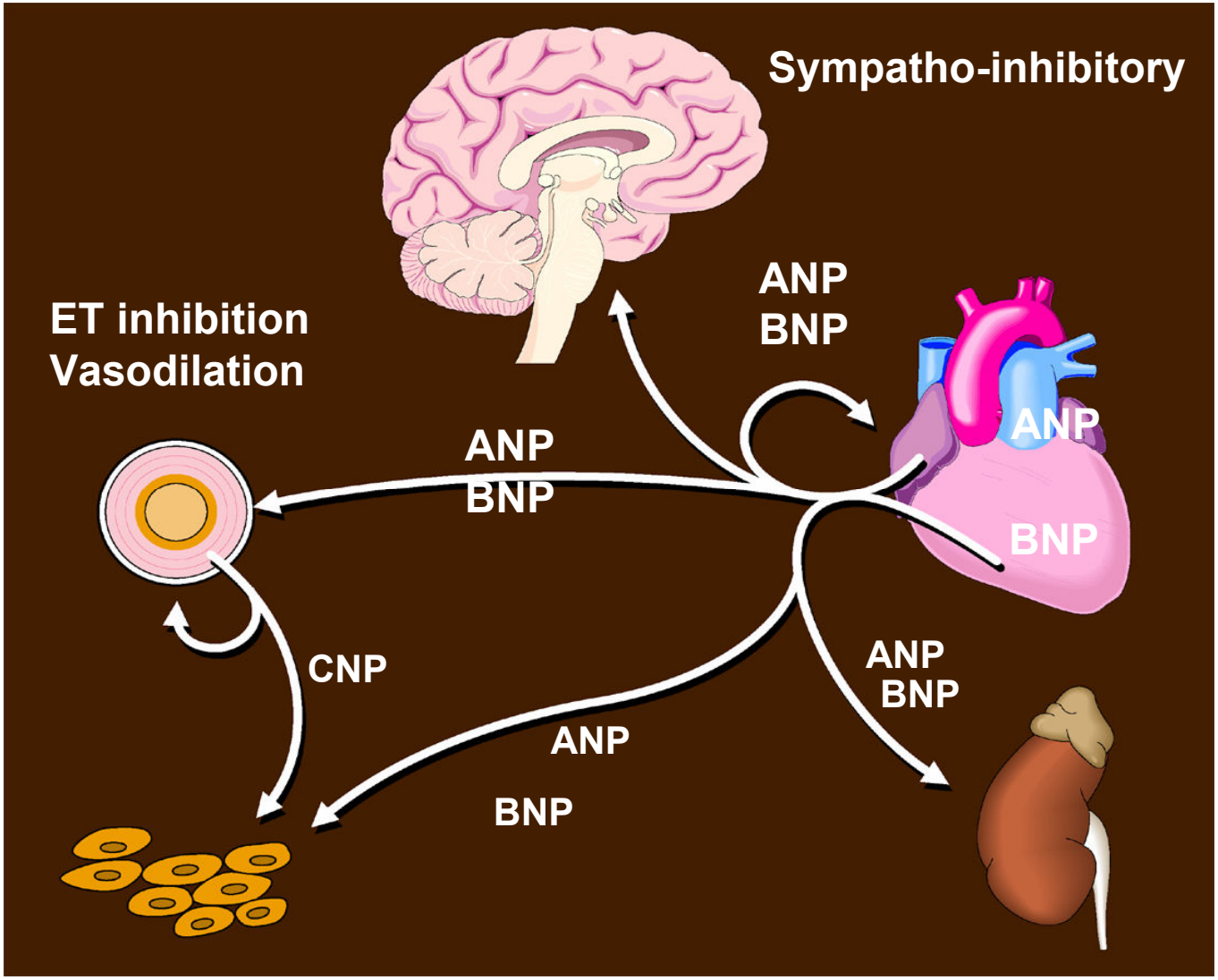
- "U-shape" curve effect
- "Tolerance" especially when iv high dose

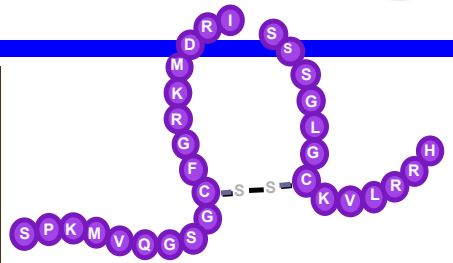
  → limit effectiveness to 16-24h only
- Dose
  - Glyceryl nitrae: 20μg/min → ↑to 200μg/min
  - ISDN: 1-10mg/h
  - DC if BP<90-100mmHg
  - Practical target: ↓10mmHg of mean BP

Nesiritide

- Recombinant BNP
  - a new vasodilator, no inotropic effect
  - v, a. and CA vasodilation → ↓pre- and after-load, ↑CO
- Cause hypotension
- Some non-responder
- Hemodynamically improve, but clinical outcome?
- Dose
  - 0.3μg/min → up-titrate to 1μg/kg/min → to 5μg/min

Natriuretic Peptide System





Anti-fibrotic
Lusitropic
Vasodilation
•veins
•arteries
•coronaries
•pulmonary

Aldosterone
inhibition

Antiproliferation
effect

Natriuresis
Renin inhibition

Nesiritide

ADHERE

Table 4. Mortality Odds Ratios in Pair-Wise Treatment Comparisons

Analysis*	NTG (n = 6,055) vs. MIL (n = 1,660)	NTG (n = 5,713) vs. DOB (n = 3,478)	NES (n = 4,663) vs. MIL (n = 1,534)	NES (n = 4,270) vs. DOB (n = 3,301)	NES (n = 4,402) vs. NTG (n = 5,668)	DOB (n = 3,656) vs. MIL (n = 1,496)
Unadjusted	0.34 (0.28–0.41)†	0.24 (0.20–0.28)†	0.53 (0.44–0.64)†	0.37 (0.32–0.44)†	1.64 (1.38–1.94)†	1.39 (1.15–1.68)†
Adjusted for covariates‖	0.69 (0.54–0.88)†	0.46 (0.38–0.57)†	0.59 (0.48–0.73)†	0.47 (0.39–0.56)†	0.95 (0.78–1.16)‡	1.27 (1.04–1.56)§
Adjusted for covariates and propensity score¶	0.69 (0.53–0.89)†	0.46 (0.37–0.57)†	0.59 (0.48–0.73)†	0.47 (0.39–0.56)†	0.94 (0.77–1.16)‡	1.24 (1.03–1.55)§

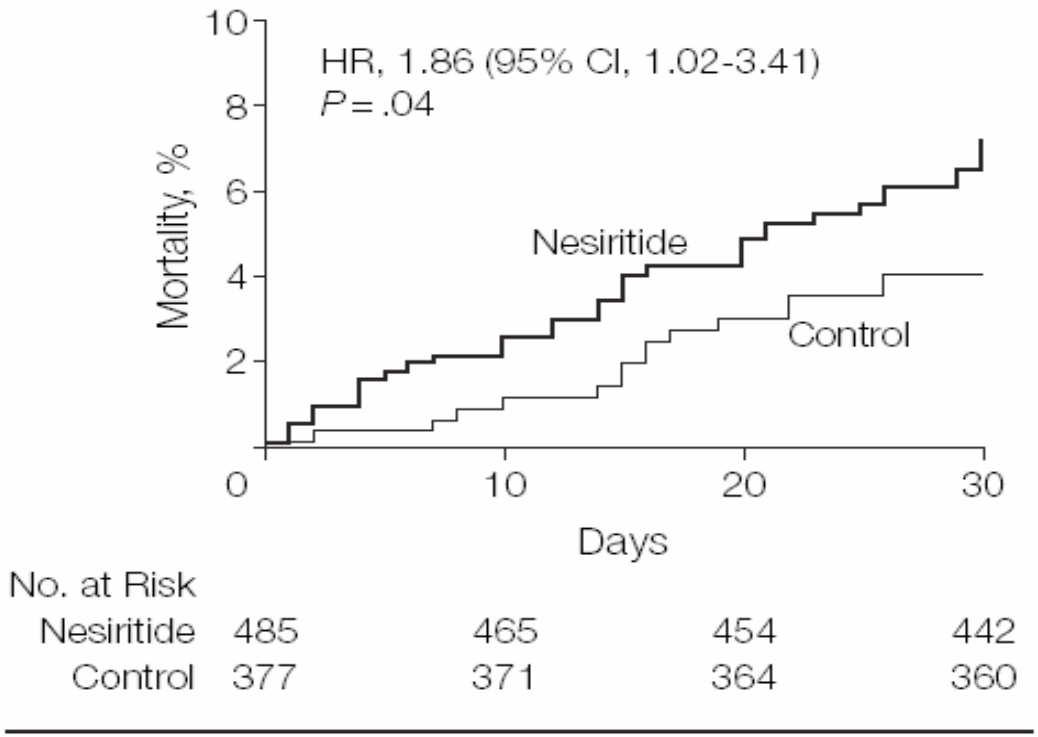
JACC 2005;46:57-64.

The risk of in-hospital mortality was similar for nesiritide and nitroglycerin.

Positive inotropic agents should be considered only in patients who are refractory to treatment with vasodilators or nesiritide or in patients in impending cardiogenic shock.

Nesiritide

Meta-analysis



Kaplan-Meier Curves of 30-Day Mortality associated With Control and Nesiritide Therapies Based on **NSGET, VMAC, and PROACTION Studies**

Nesiritide may be associated with an increased risk of death after treatment for acutely decompensated heart failure.

Large-scale controlled trial before routine use of nesiritide for ADHF.

JAMA 2005;293:1900-1905.

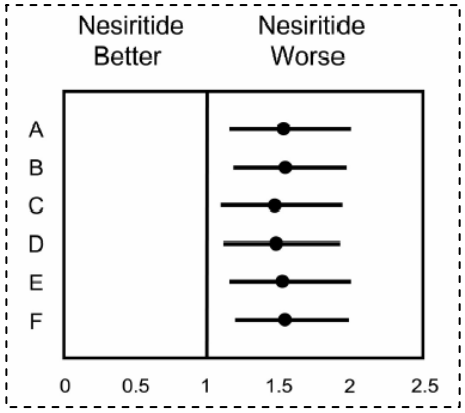
Nesiritide

Meta-analysis

TABLE 4. Effect of Nesiritide on Development of Worsening Renal Function in Patients With Acutely Decompensated Heart Failure

	Events, n/N (%)			
	Nesiritide	Control	RR_{MH} (95% CI)	*P*
Nesiritide ≤0.03 vs non-inotrope based controls	134/610 (22)	60/389 (15)	1.52 (1.16–2.00)	0.003
Nesiritide ≤0.03 vs all control therapies, including inotropes	163/772 (21)	69/472 (15)	1.54 (1.19–1.98)	0.001
Nesiritide ≤0.015 vs non-inotrope based controls	100/442 (23)	60/389 (15)	1.46 (1.09–1.95)	0.012
Nesiritide ≤0.015 vs all control therapies, including inotropes	99/464 (21)	69/472 (15)	1.47 (1.12–1.93)	0.006
Nesiritide ≤0.06 vs non-inotrope based controls	140/635 (22)	60/389 (15)	1.53 (1.16–2.00)	0.002
Nesiritide ≤0.06 vs all control therapies, including inotropes	169/797 (21)	69/472 (15)	1.54 (1.20–1.99)	0.001

Nesiritide doses refer to infusion rates ($\mu g \cdot kg^{-1} \cdot min^{-1}$) that followed bolus administration.



Nesiritide significantly increases the risk of worsening renal function in patients with ADHF.

Circulation 2005;111:1487-1491.

Suggested Use of Nesiritide in the ED

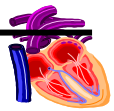
Consider nesiritide as an alternative to nitroglycerin in the patient with NYHA class III/IV ADHF patient and:
- Moderate respiratory distress
- Use of i.v. nitroglycerin is contraindicated:
  - OU patients with unsatisfactory response to standard therapy (when nitroglycerin can not be used in the protocol)
  - Telemetry/floor admission
- Tachycardia, serious atrial/ventricular dysrhythmia, or ventricular irritability
- Identification as a candidate by future studies confirming preliminary findings—potentially those with systolic dysfunction and SBP > 160 mm Hg

Avoid nesiritide in the patient with acute decompensation of heart failure and:
- Inadequate time to gauge response to standard therapy
- Severe respiratory distress and impending intubation
- Cardiogenic shock
- Responding to standard therapy
- On i.v. nitroglycerin with well controlled BP
- RV myocardial infarction
- Aortic stenosis
- Constrictive pericarditis
- Hypertrophic obstructive cardiomyopathy

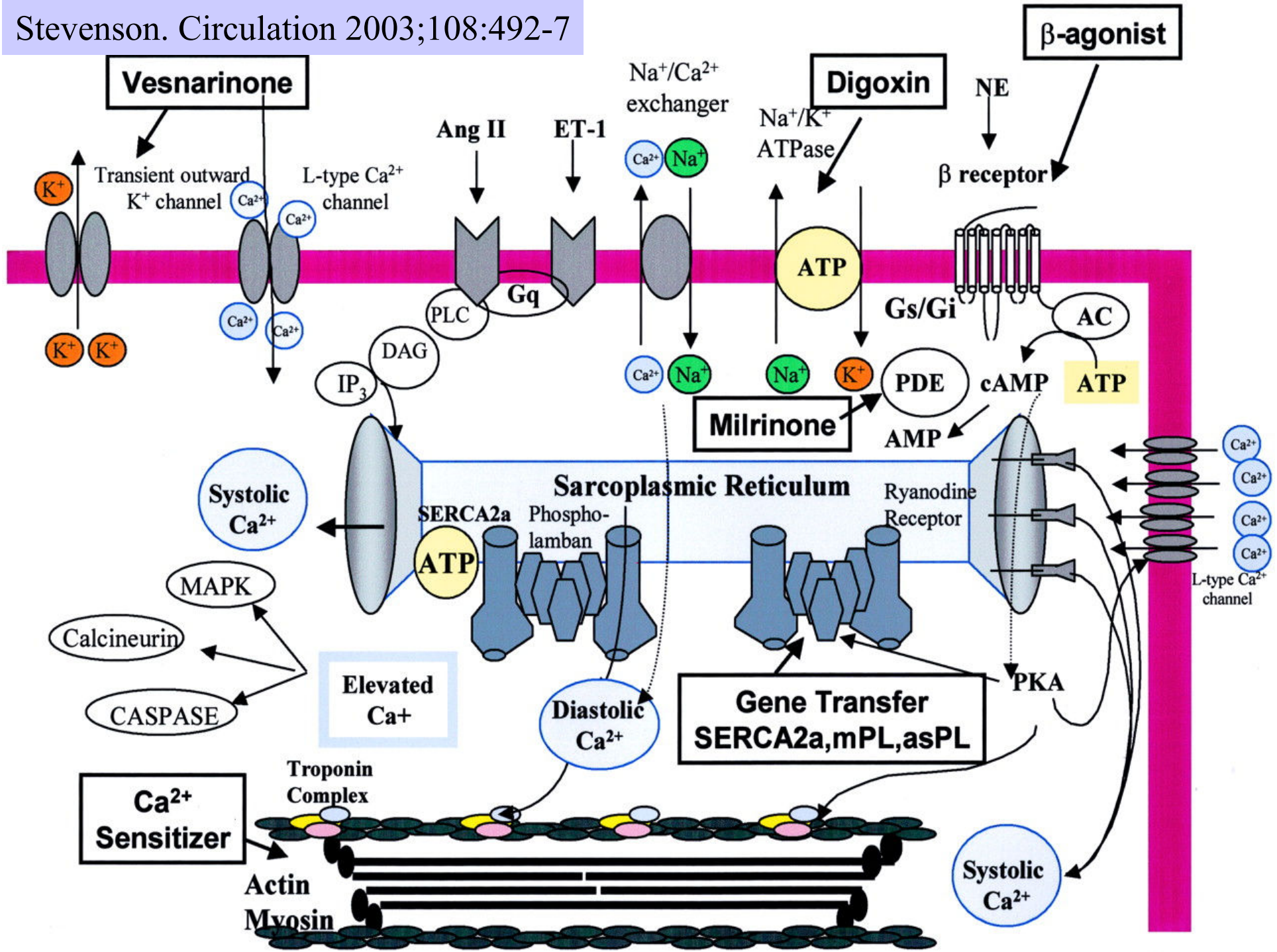
Inotropic Agents

Administration of positive inotropic agents

	Bolus	Infusion rate
Dobutamine	No	2 to 20 μg/kg/min (β+)
Dopamine	NO	<3 μg/kg/min: renal effect (δ+) 3-5 μg/kg/min: intropic(β+) >5 μg/kg/min: (β+), vasopressor(α+)
Milrinone	25-75 μg/kg over 10-20 min	0.375-0.75 μg/kg/min
Enoximone	0.25-0.75 mg/kg	1.25-7.5 μg/kg/min
Levosimendan	12-24 μg/kg[a] over 10 min	0.1 μg/kg/min which can be decreased to 0.02 or increased to 0.2 μg/kg/min
Norepinephrine	No bolus	0.2-1.0 μg/kg/min
Epinephrine	Bolus: 1mg can be given IV. at resuscitation, may be repeated after 3-5 min, endotracheal route is not favoured	0.05-0.5 μg/kg/min



Stevenson. Circulation 2003;108:492-7



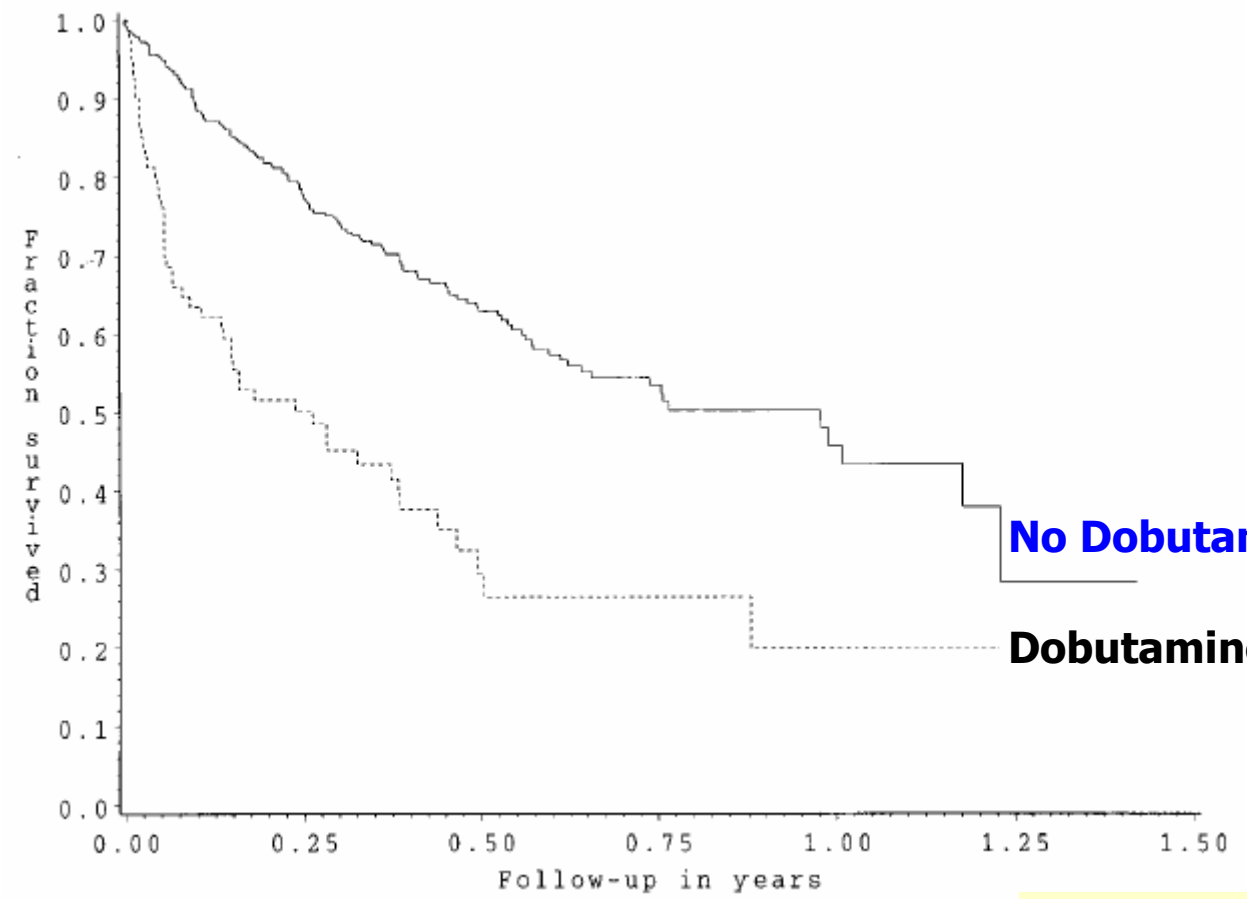
Positive inotropic drugs

cAMP dependent agents

cAMP independent agents

Dobutamine

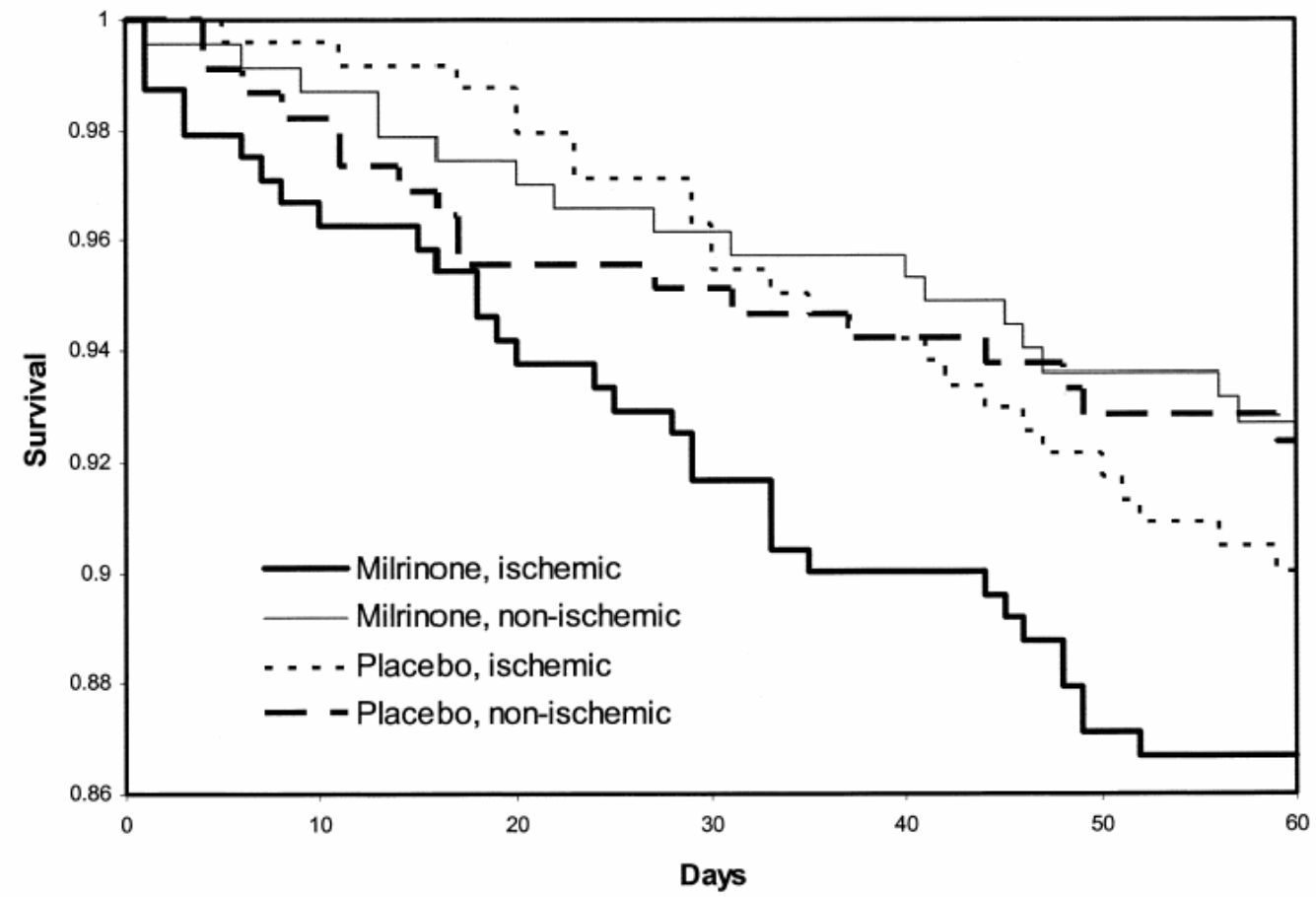
FIRST



Am Heart J 1999;138:78-86.

Milrinone

OPTIME-CHF



JACC 2003;41:997-1003.

Positive inotropic drugs

cAMP dependent agents

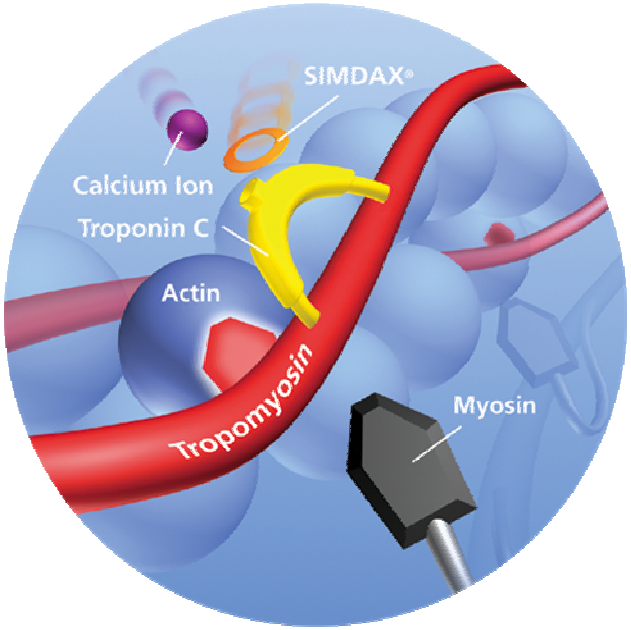
- **β-adrenergic agonists**
  - Epinephrine, Dobutamine
- **Dopaminergic agonists**
  - Dopamine, Dopexamine
- **Phosphodiesterase inhibitors**
  - Milrinone, Inamrinone

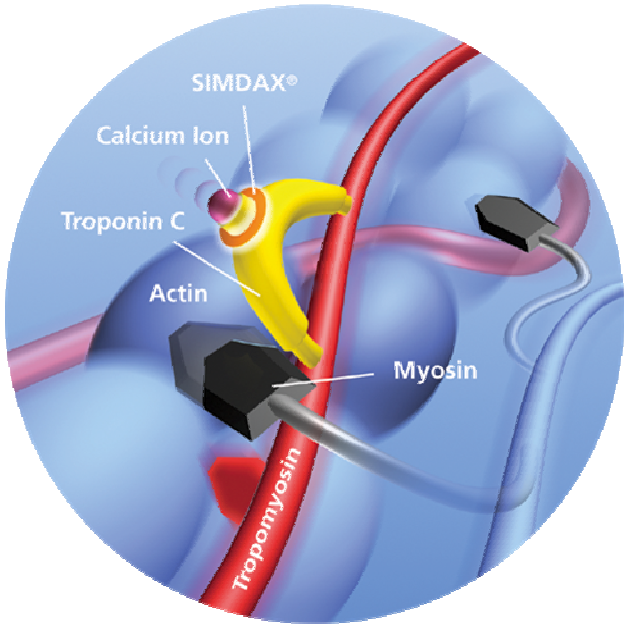
cAMP independent agents

- **Cardiac glycosides**
- **Calcium salts**
- **Liothyronine (T_3)**
- **α-AR agonists**

Levosimendan: Calcium Sensitisation

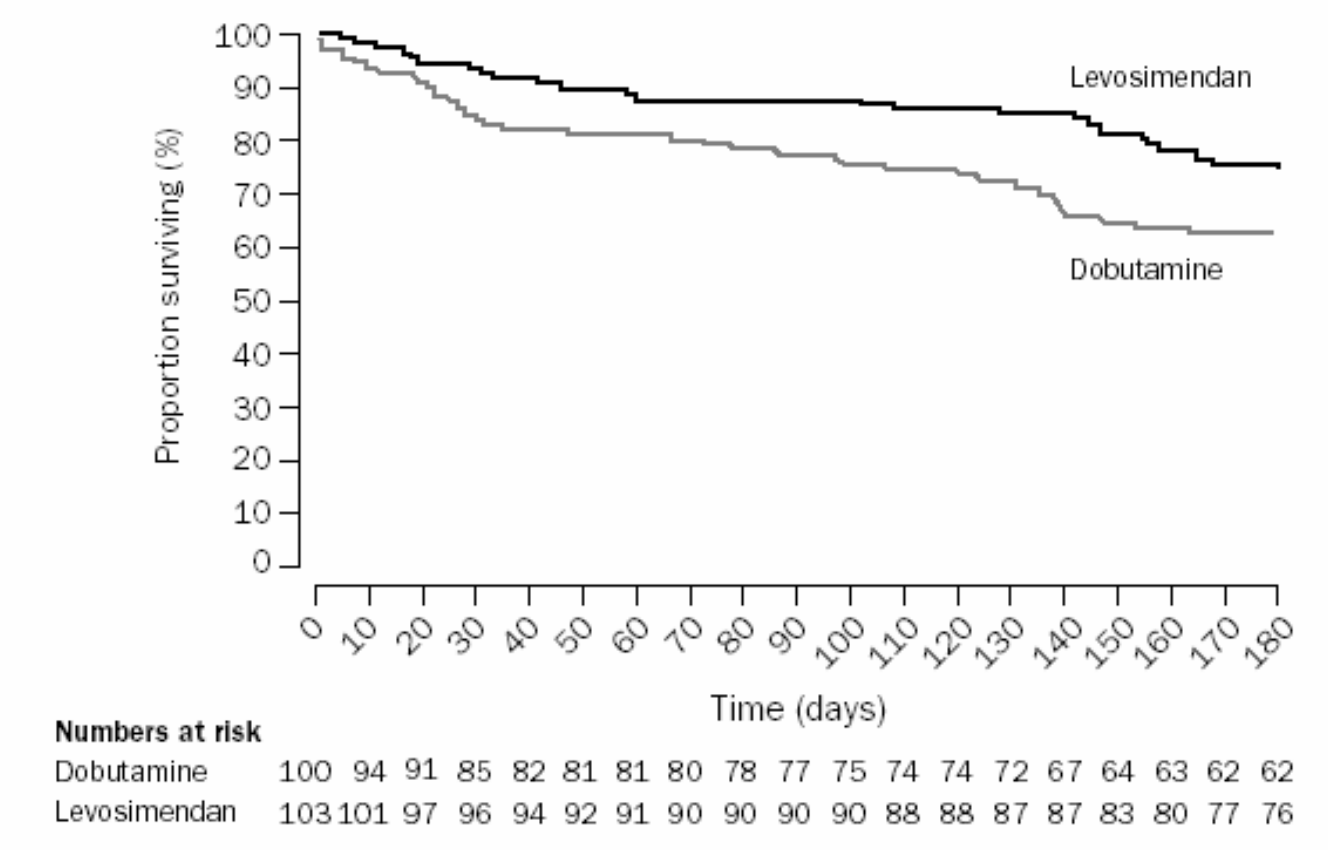
- Enhanced contractility of myocardial cell by amplifying trigger for contraction with no change in total intracellular Ca^{2+}





Dobutamine

LIDO



Numbers at risk

Dobutamine	100	94	91	85	82	81	81	80	78	77	75	74	74	72	67	64	63	62	62
Levosimendan	103	101	97	96	94	92	91	90	90	90	90	88	88	87	87	83	80	77	76

Lancet 2002 ;360:196-202.

추계 순환기학회 2007 심부전

Levosimendan

Meta-analysis: *levosimendan vs. placebo, long-term*

b

- **The hemodynamic effects of the levosimendan support its use in acute and postoperative heart failure.**
- **Several moderatesize trials (LIDO, RUSSLAN, CASINO) have previously suggested that the drug might even improve the prognosis of patients with decompensated heart failure. These trials were carried out in patients with high filling pressures.**
- **Recently two larger trials (SURVIVE and REVIVE) in patients who were hospitalized because of worsening heart failure have been finalized. These trials did not require filling pressures to be measured. The two trials showed that levosimendan improves the symptoms of heart failure, but does not improve survival.**

Exact

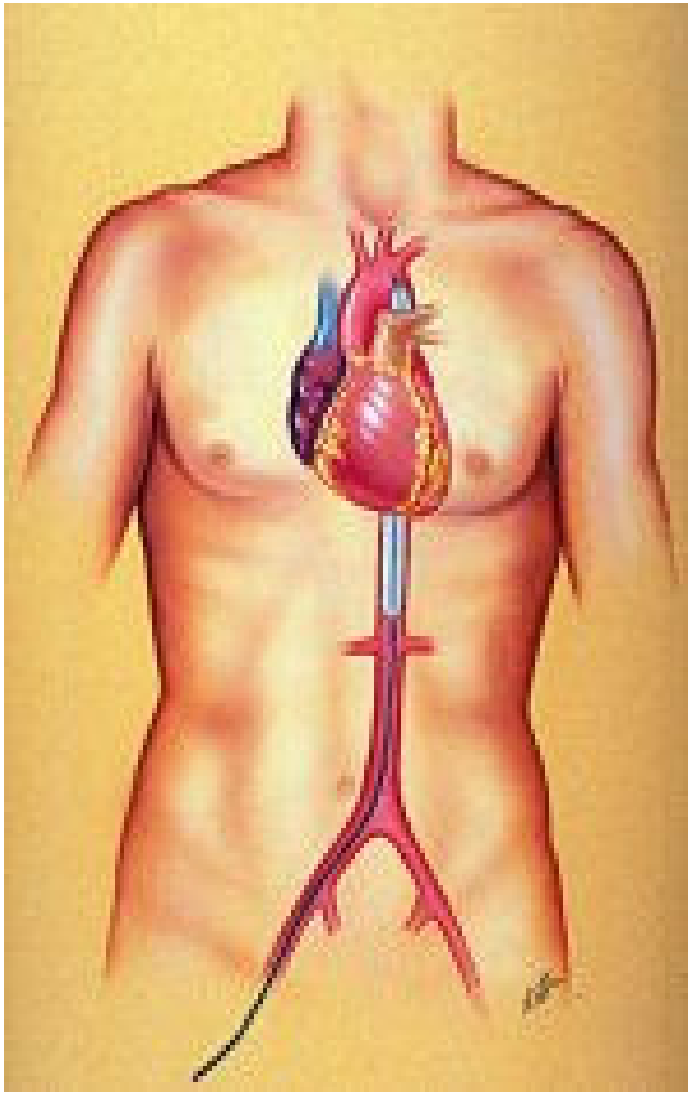
Ra

Heterogeneity = 9.868768 (df = 3) P = 0.0197

Mechanical Support

- **Intra-aortic balloon pump (IABP)**
  - used as bridge to TP or myocardial ischemia
  - placed into high descending thoracic aorta
  - balloon counterpulsation
    - inflates during diastole - ↑ coronary perfusion
    - deflates w/ aortic valve opening - ↓ arterial impedence
- **Left ventricular assist device (LVAD)**
  - extracorporeal vs implantable
  - allows ambulation and even discharge
  - operative mortality 10-15%
  - requires continuous anticoagulation

Intra-aortic balloon pump



Left ventricular assist device

Conclusions

- While the treatment of **CHF** relies mainly on neurohumoral interventions, successful management of **ADHF** depends on the hemodynamic interventions.

- Treatment should be performed according to the principles introduced in the guidelines for the diagnosis and treatment of acute heart failure.

- Additional studies are needed to determine the effect of new agents on rates of morbidity and mortality in ADHF.