The Management of Acute Decompensated Heart Failure

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Acute Decompensated Heart Failure (ADHF)

- Definition
  : Rapid onset of symptom and signs secondary to abnormal cardiac function
- Cardiac dysfunction
  : systolic or diastolic dysfunction
  : arrhythmia
  : preload and afterload mismatch
- Increase in the number of hospitalization and high mortality
- Often life threatening and require urgent treatment

Significant Clinical and Economic Burden of HF

- Persons with HF in US : 5.0 million
- Overall prevalence : 2.2%
- Incidence : 550,000/yr
- Mortality in 2001 : 52,828
- Cost : $25.8 billion

AHA. *Heart Disease and Stroke Statistics*—2004 Update

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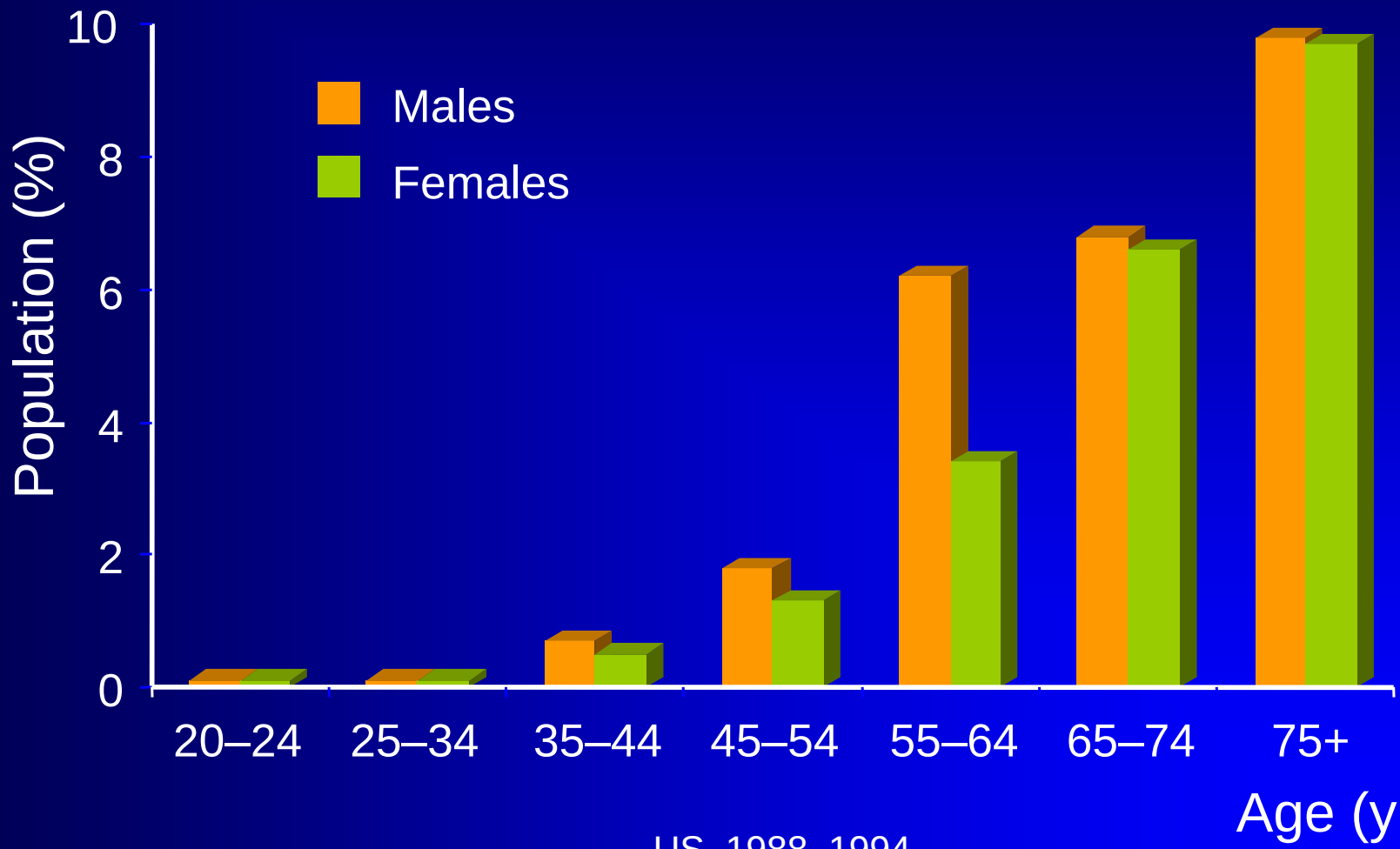
Prevalence of HF Increases with Age



US, 1988–1994

AHA. *Heart Disease and Stroke Statistics*—2004 Update

Underlying Heart Disease In KHFS

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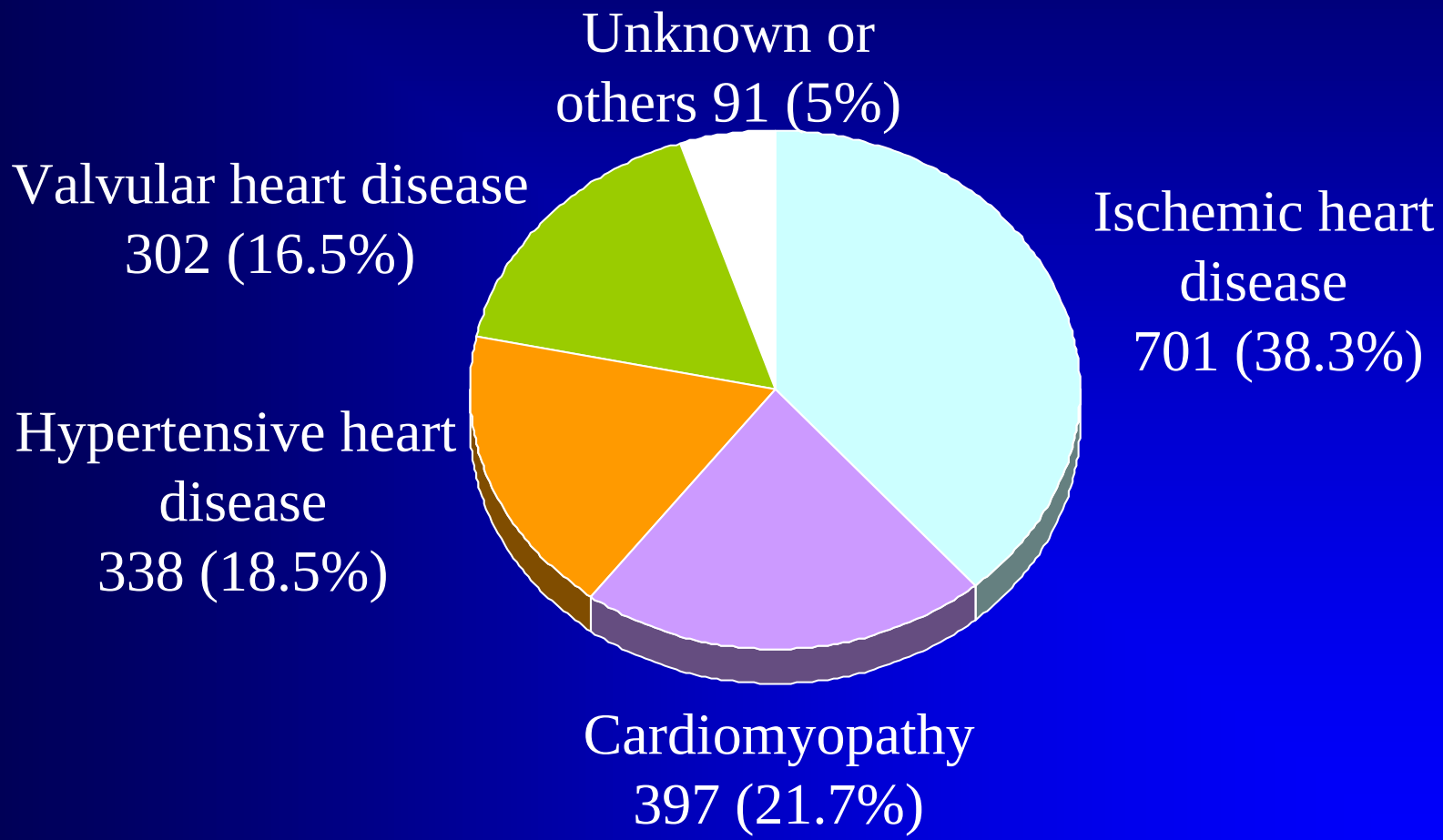

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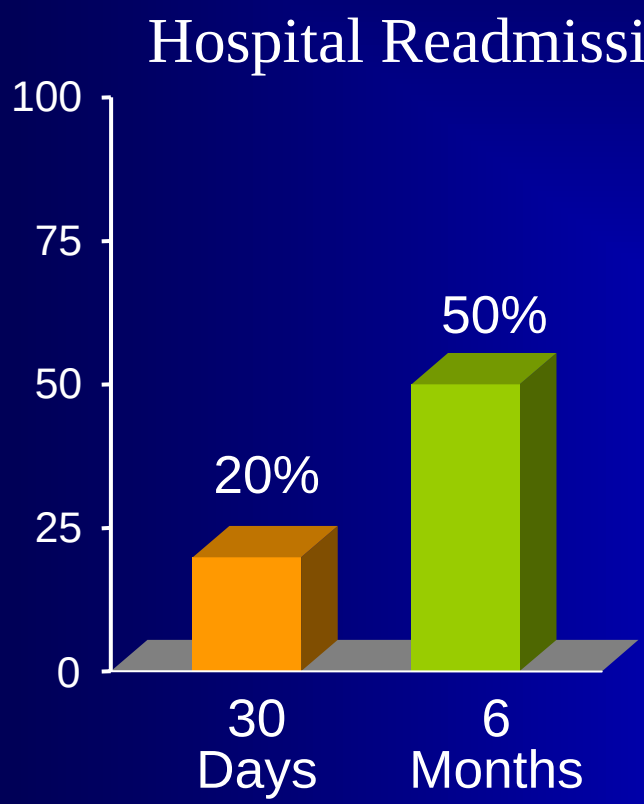
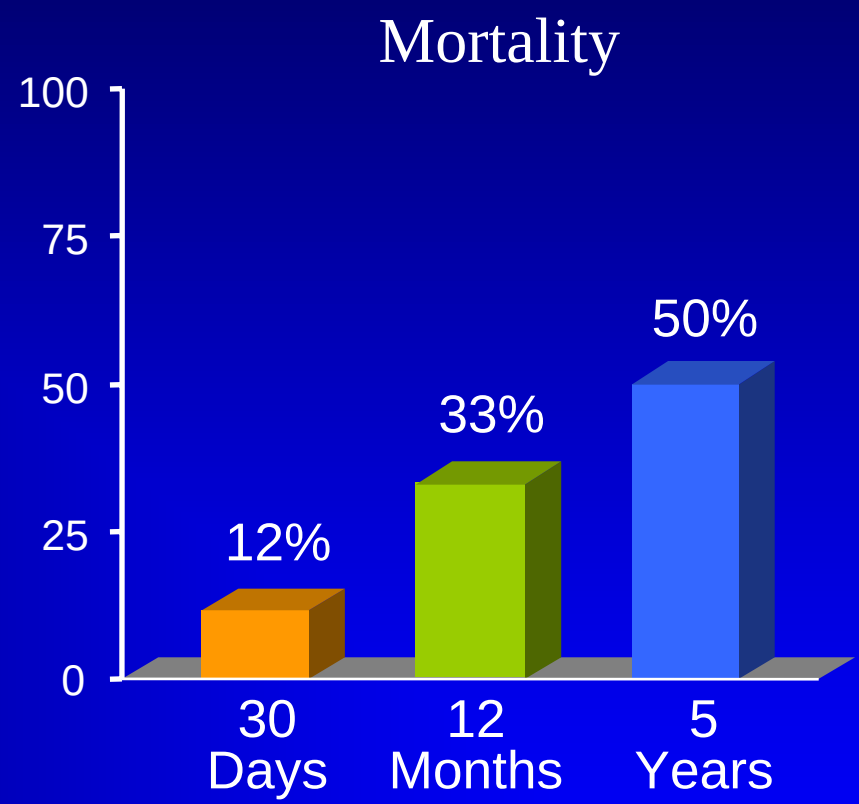
Outcomes in Patients Hospitalized With HF





Median LOS: 6 days

N = 38,702

Aghababian RV. *Rev Cardiovasc Med. 2002*;3(suppl 4):S3

Jong P et al. *Arch Intern Med. 2002*;162:1689

Cumulative Survival Rate By Underlying Heart Disease In KHFS

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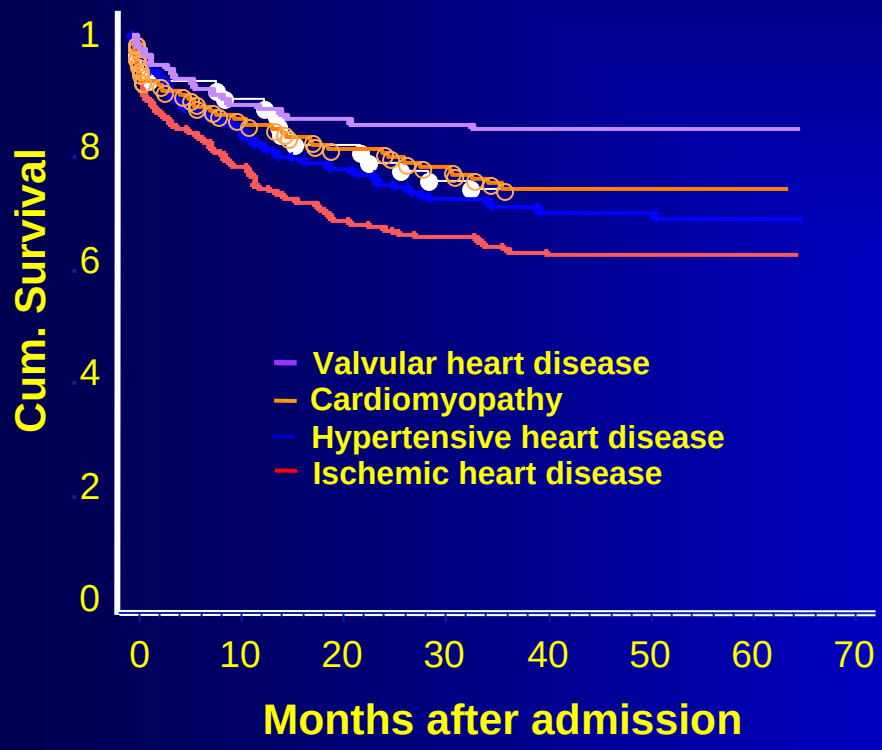

	6mo	1yr	2yr	3yr
VHD	0.926	0.874	0.834	0.830
CMP	0.915	0.845	0.803	0.718
HHD	0.908	0.825	0.789	0.700
IHD	0.794	0.702	0.612	0.607

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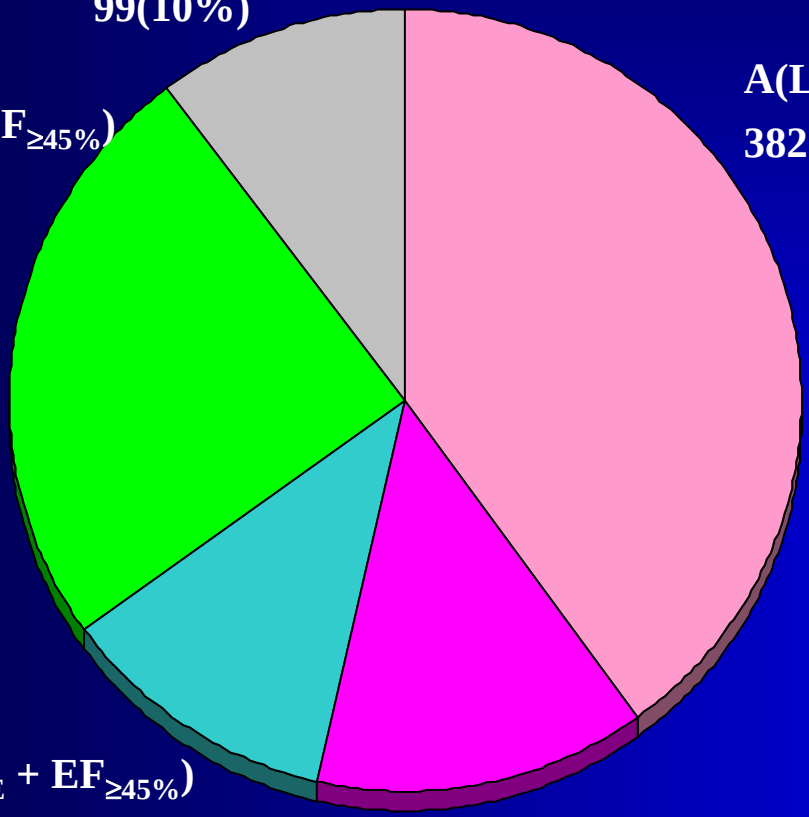
Distribution of LV Dysfunction In KHFS



A+B(LVEF <40%) : 513 (54%)

C+D(LVEF ≥45%) : 345 (36%)

Clinical status of ADHF

I : Acute decompensated heart failure with symptom

II : Hypertensive AHF
hypertension/hypertensive crisis and
preserved LV function

III: Acute heart failure with pulmonary edema
severe respiratory distress (O2 saturation<90%)

Clinical status of ADHF

IV : Cardiogenic shock

SBP<90mmHg, drop of mean BP > 30mmHg,

low urine output (<0.5ml/kg/h),
pulse rate > 60BPM

V : High output failure

high heart rate, warm peripheral,
pulmonary congestion

VI : Right sided acute heart failure

low output syndrome, ↑ JVP,
congestion, hypotension

Clinical status and Precipitating factors

- I : Acute decompensated heart failure with mild symptom
  - pre-existing HF (cardiomyopathy)
  - acute severe myocarditis
  - postpartum cardiomyopathy
- II : Hypertensive AHF
  - Hypertensive crisis
- III : Acute heart failure with pulmonary edema
  - Valvular regurgitation
  - Severe AS

Clinical status and Precipitating factors

- IV : Cardiogenic shock
  - acute coronary syndrome

- V : High output
  - septicemia
  - thyrotoxicosis
  - anemia

- VI : Right sided acute heart failure
  - asthma
  - RV infarction

Mechanism of Reversibility in ADHF

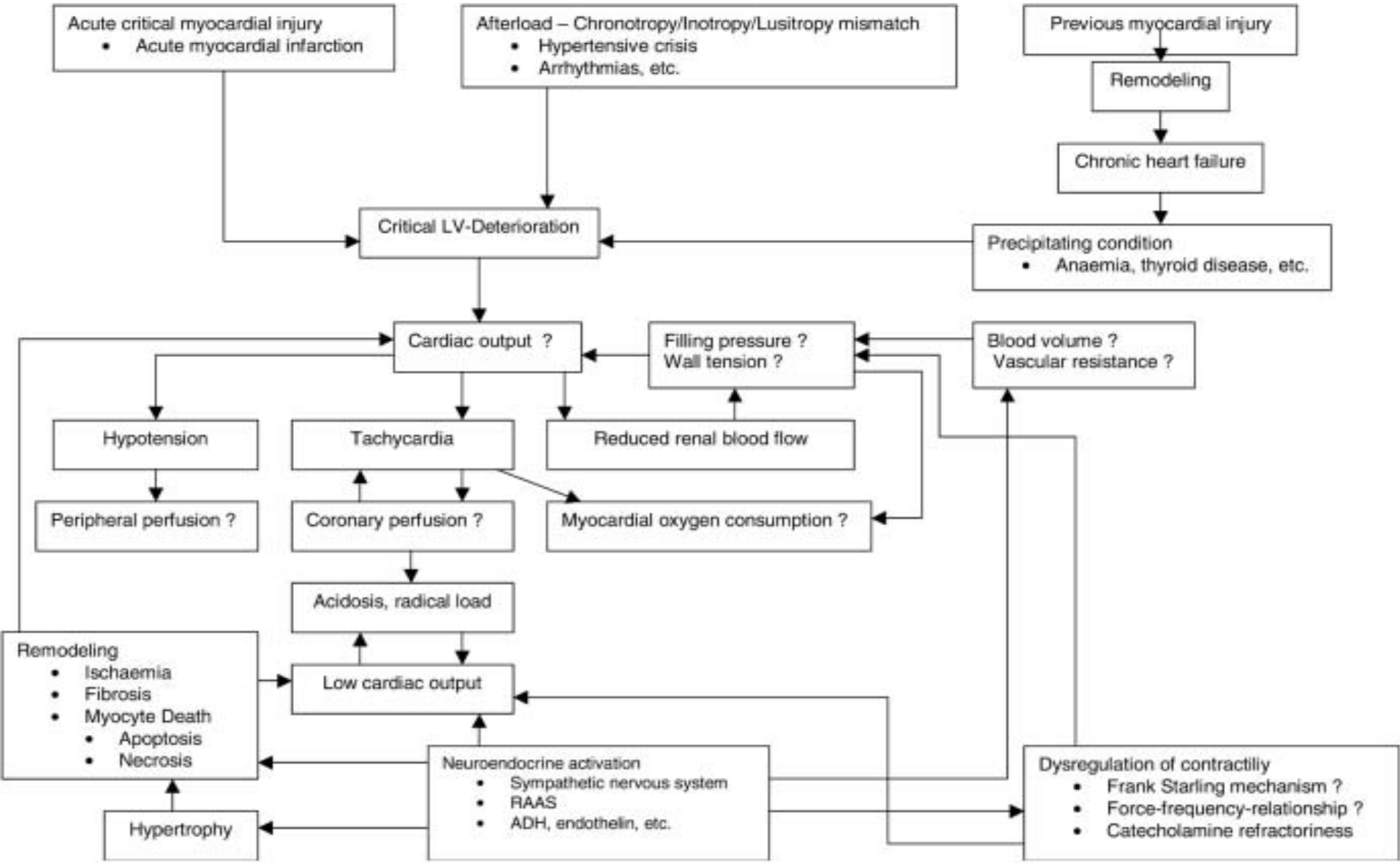
- Normalized LV function after the optimal management of ADHF

- Reversible LV dysfunction
  - respond to treatment
  - especially, ischemia, stunning, hibernation

Reversibility of ADHF

- Control hypertension
- Coronary revascularization (PCI, CABG)
- Valvuloplasty, replacement
- Mechanical assist device (VAD)
- Control the precipitating factor of ADHF
  - anemia, thyrotoxicosis, sepsis

Pathophysiology of ADHF



ESC guideline of acute heart failure, European heart journal 2005;26:384-416

Diagnostic tools of ADHF

- Clinical evaluation

  - assess peripheral circulation, temperature

  - JVP

  - chest auscultation

  - cardiac palpation, auscultation

  - abdominal and carotid bruit

Diagnostic tools of ADHF

- EKG
- Chest X-ray and imaging techniques
- Echocardiography
- Laboratory test

Laboratory test

Blood count	Always
Platelet count	Always
Urea and Electrolytes (Na^+, K^+, Urea, Creatinine)	Always
Blood glucose	Always
CKMB, cardiac TnI/TnT	Always
CRP	Always
D-dimer	Always (may be falsely positive if CRP elevated or patient has been hospitalized for prolonged period)

Laboratory test

INR	If patient anticoagulated or in severe heart failure
Arterial blood gases	In severe heart failure, or in diabetic patients
Transaminases	To be considered
Urinanalysis	To be considered
Plasma BNP or NTproBNP	To be considered

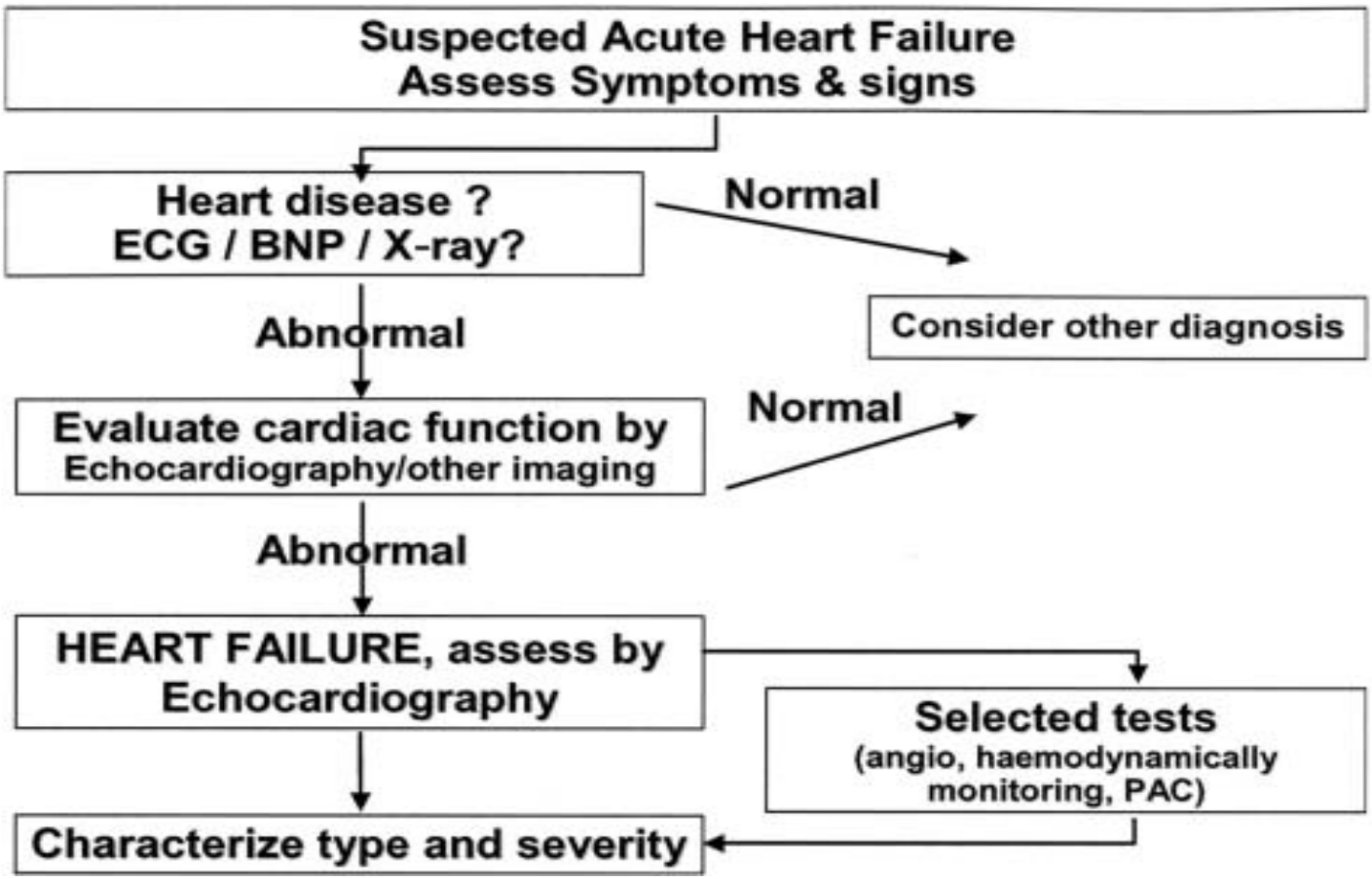
Plasma B-type natriuretic peptide (BNP)

- Reflect the LV wall stretch and volume overload
- Exclude and/or identify CHF for dyspnea
- Good negative predictive value to exclude HF

Plasma B-type natriuretic peptide (BNP)

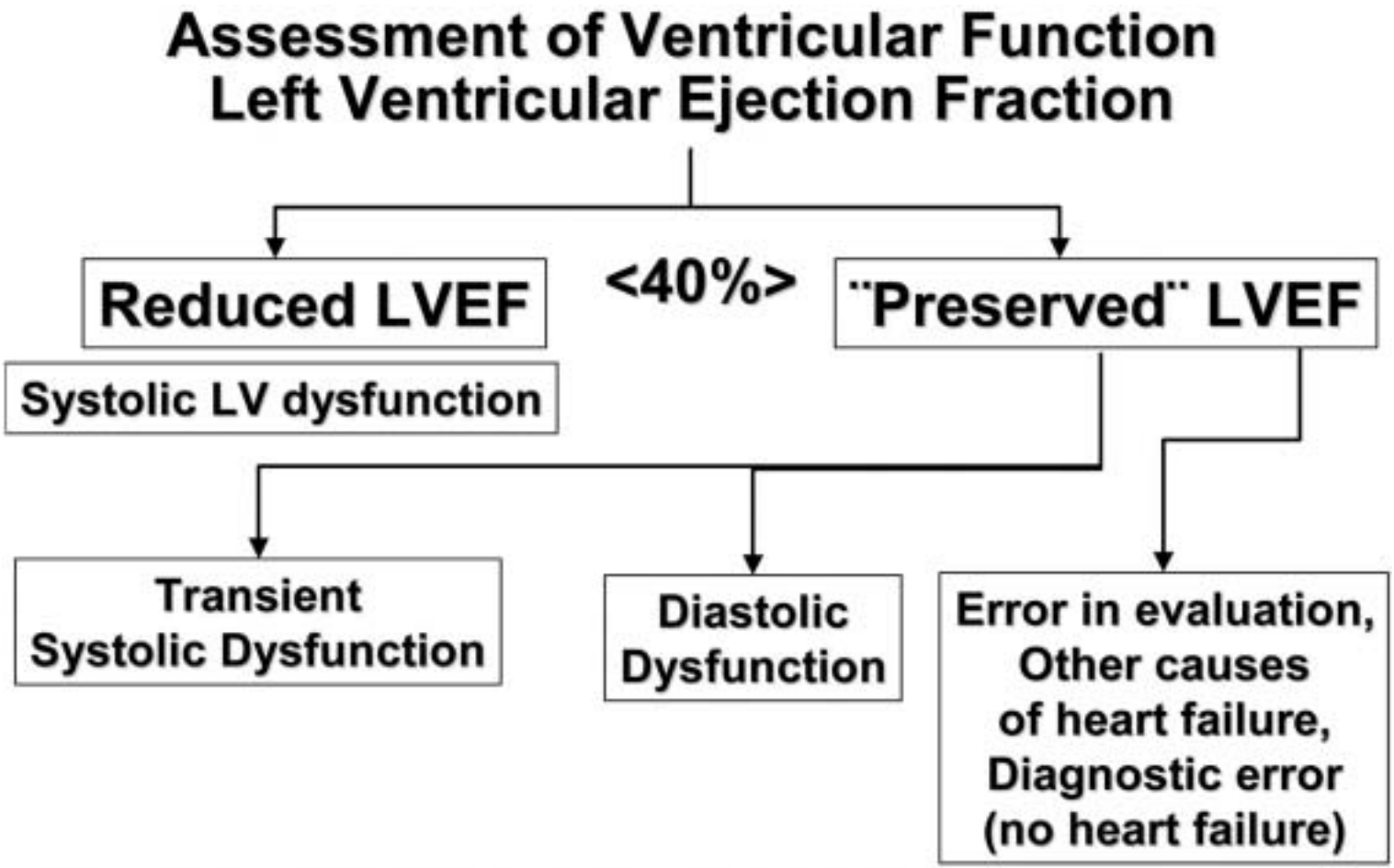
- Decision cut point
  - 300 pg/ml (NT-proBNP)
  - 100 pg/ml (BNP)
- Influenced by various condition (renal failure, sepsis)
- Important prognostic information in ADHF

Diagnosis of ADHF



ESC guideline of acute heart failure, European heart journal 2005;26:384-416

Assessment of LV function



ESC guideline of acute heart failure, European heart journal 2005;26:384-416

Treatment Goals

Clinical

↓ symptoms (dyspnea and/or fatigue)

↓ clinical signs

↓ body weight

↑ diuresis

↑ oxygenation

Treatment Goals

Laboratory

- Serum electrolyte normalization
- ↓ BUN and/or creatinine
- ↓ S-bilirubin
- ↓ plasma BNP
- Blood glucose normalization

Treatment Goals

Hemodynamic

PCWP < 18 mmHg

↑ cardiac output and/or stroke volume

Right atrial pressure ≤ 8mmHg

SVR : 1000-1200 dynes sec cm^{-5}

Treatment Goals

Outcome

↓ length of stay in the intensive care unit

↓ duration of hospitalization

↑ time to hospital re-admission

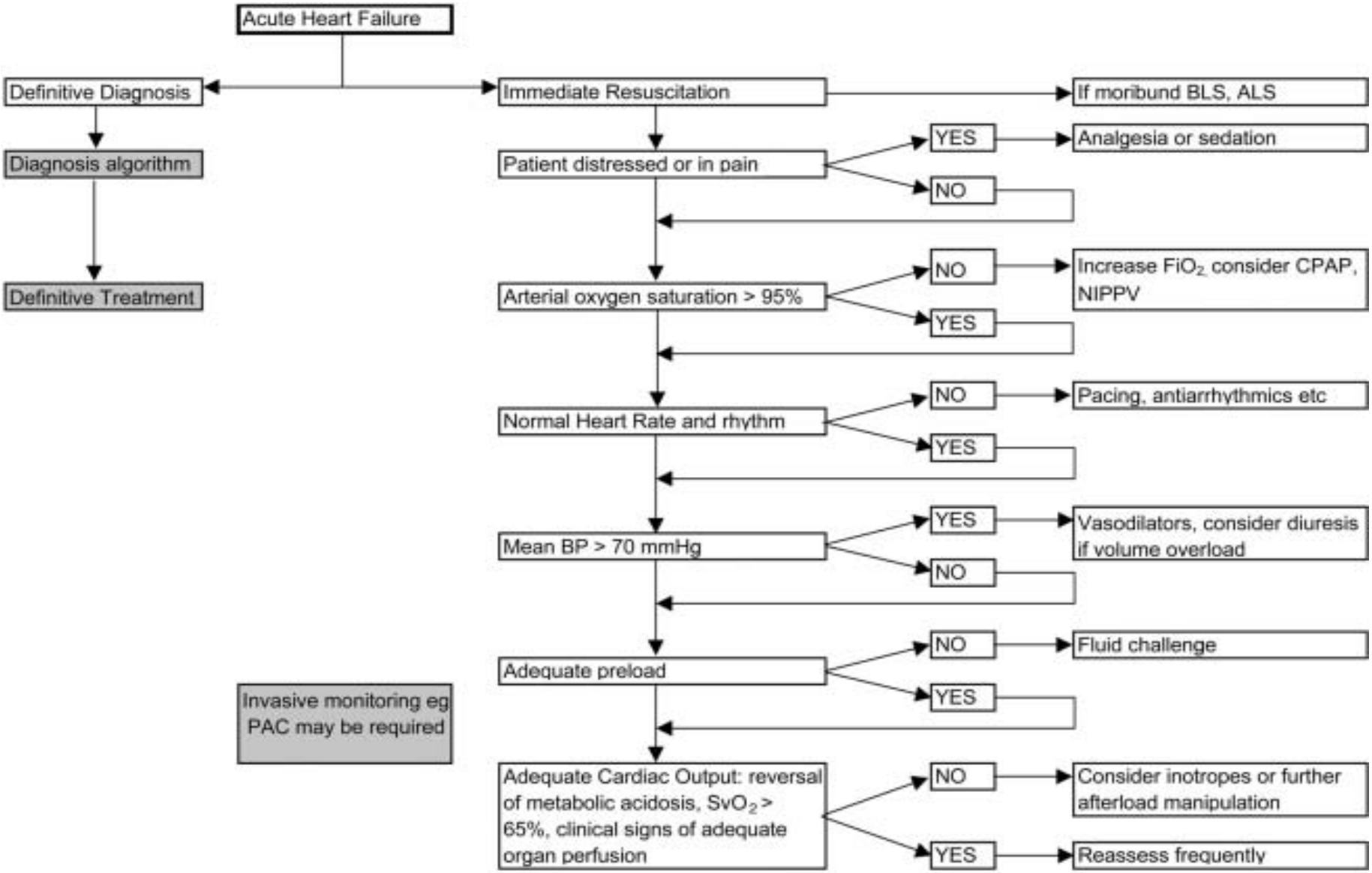
↓ mortality

Tolerability

Low rate of therapeutic withdrawal

Low incidence of adverse effects

Immediate goal of treatment



ESC guideline of acute heart failure, European heart journal 2005;26:384-416

Evidence of congestion and low perfusion

Evidence for Congestion

Orthopnea

JVD

Edema

Ascites

Rales

Abd-jugular reflex

Evidence for low perfusion

Narrow pulse pressure

Cool extremities

May be sleepy, obtunded

Worsening renal function

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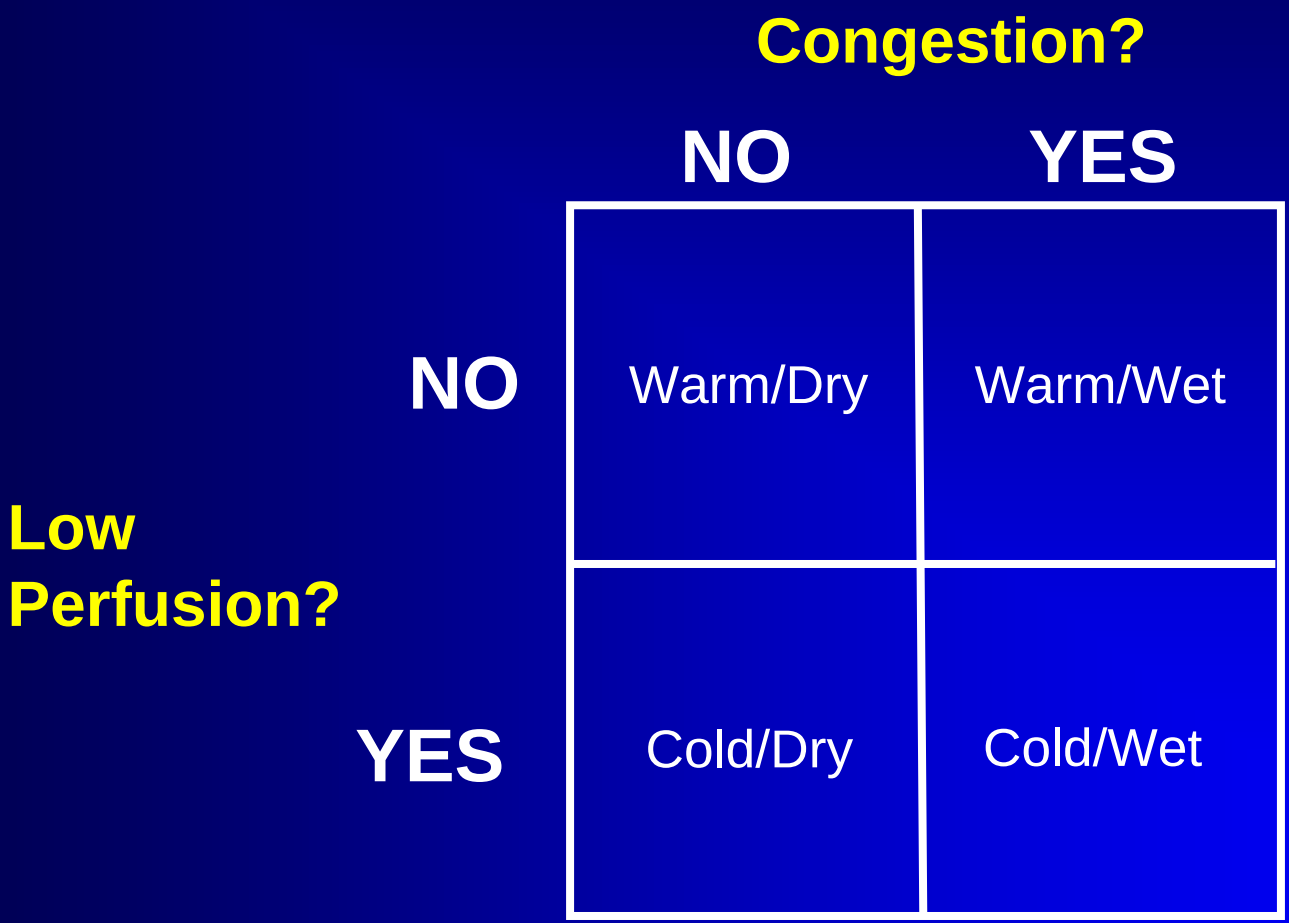
Assessment of Hemodynamic Profile



Adapted from LW Stevenson

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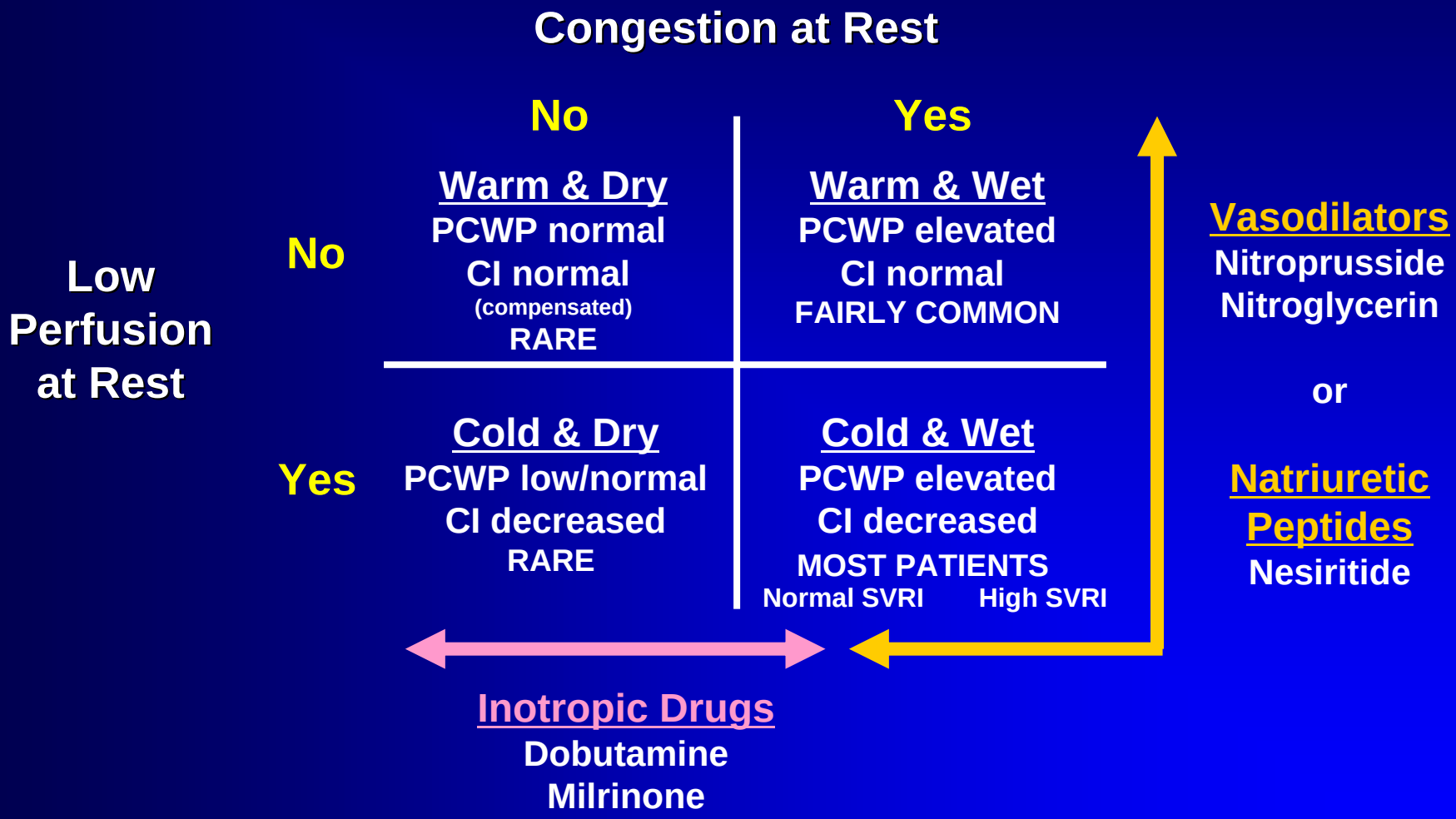
Patient Selection and Treatment



Fonarow GC. *Rev Cardiovasc Med.* 2001;2(suppl 2):S7–S12.

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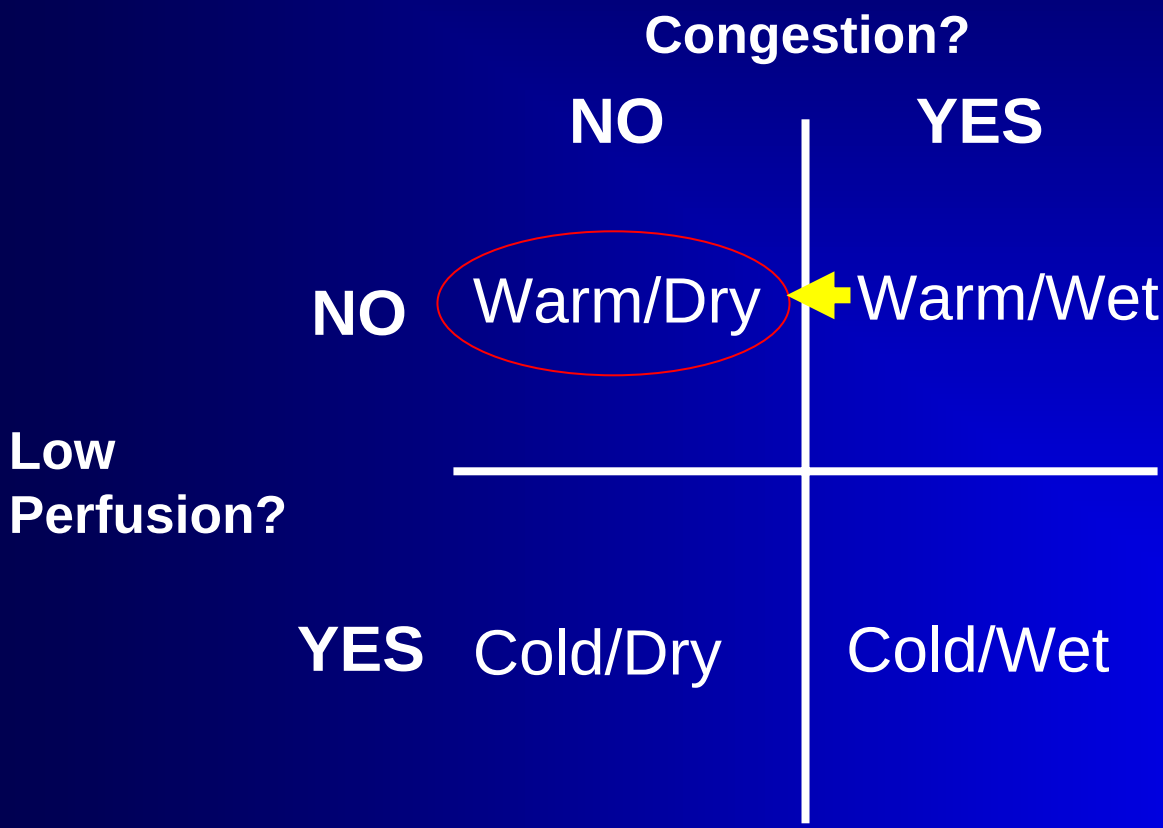
Treatment Options based on Hemodynamic Profile



DRY OUT

Diuresis

Nesiritide

Nitroprusside

Adapted from LW Stevenson

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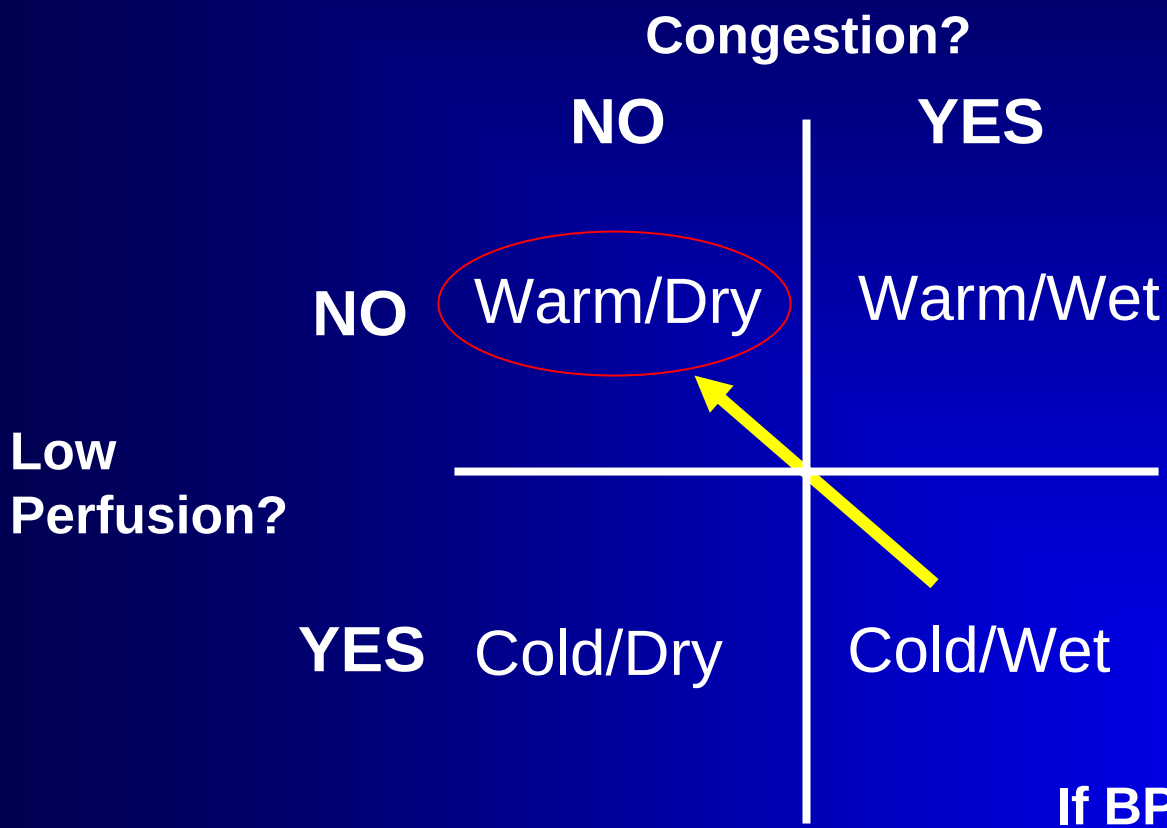
Treatment Options based on Hemodynamic Profile



Maintain BP and DRY OUT

If BP >90
Nesiritide
Nitroprusside
Diuresis
+/- Inotropes

If BP <90
Inotropes
Nesiritide
Nitroprusside
Diuresis

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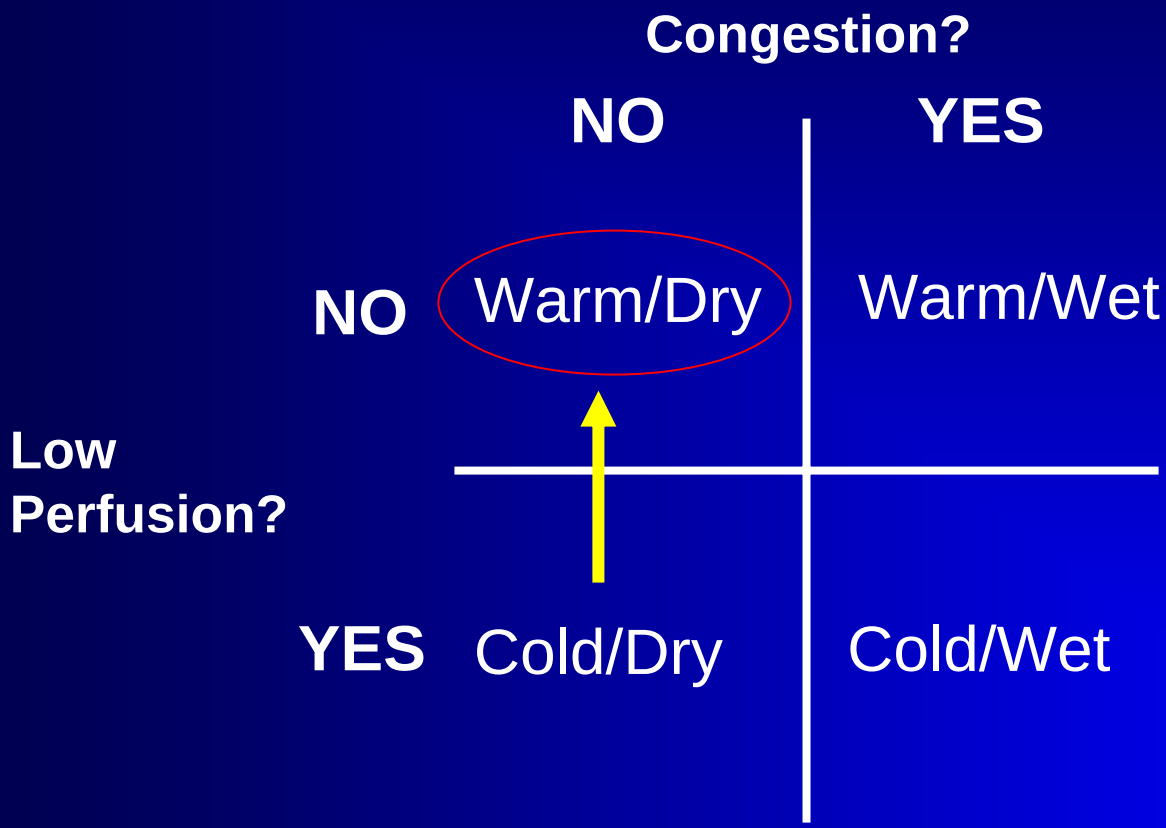
Treatment Options based on Hemodynamic Profile



Inotropes DON'T DIURESE

If BP low: Vasodilators may not be indicated

Right heart catheterization is very helpful for accurate assessment and appropriate Rx especially vasodilators

Adapted from LW Stevenson

Pharmacological and Non-pharmacological managements of ADHF

Non phamacological management

- Bed rest & salt restriction
- IABP
- Coronary intervention, CABG
- Pericardiocentesis

Non phamacological management

- Valvular replacement or plasty
- Cardiac resynchronization therapy
- VAD
- Cardiac transplantation

Pharmacological management

- Morphine
- Diuretics
- Vasodilator
- Inotropics
- others

Morphine and its analogue

- Early stage of severe ADHF
- Restless and dyspnea
- Induce venodilation and mild arterial dilation
- Reduce heart rate
- Bolus 3mg at a time and repeat, if required

Diuretics in ADHF

- Usually, loop diuretics
- Higher dose than that of optimal volume status
- Doses should be doubled if increased effect is desired

Diuretics in ADHF

- Addition of metolazone and IV thiazide in diuretic resistance
- Adequacy of oral diuretic dosing should be demonstrated prior to discharge
- Consider cardiorenal syndrome
  : ↓ renal perfusion, ↑ adrenergic system, ↑ RAS

Inotropics in ADHF

- Dobutamine
  - increased cardiac output
  - decrease SVR, pulmonary vascular resistance
  - diuretic effect

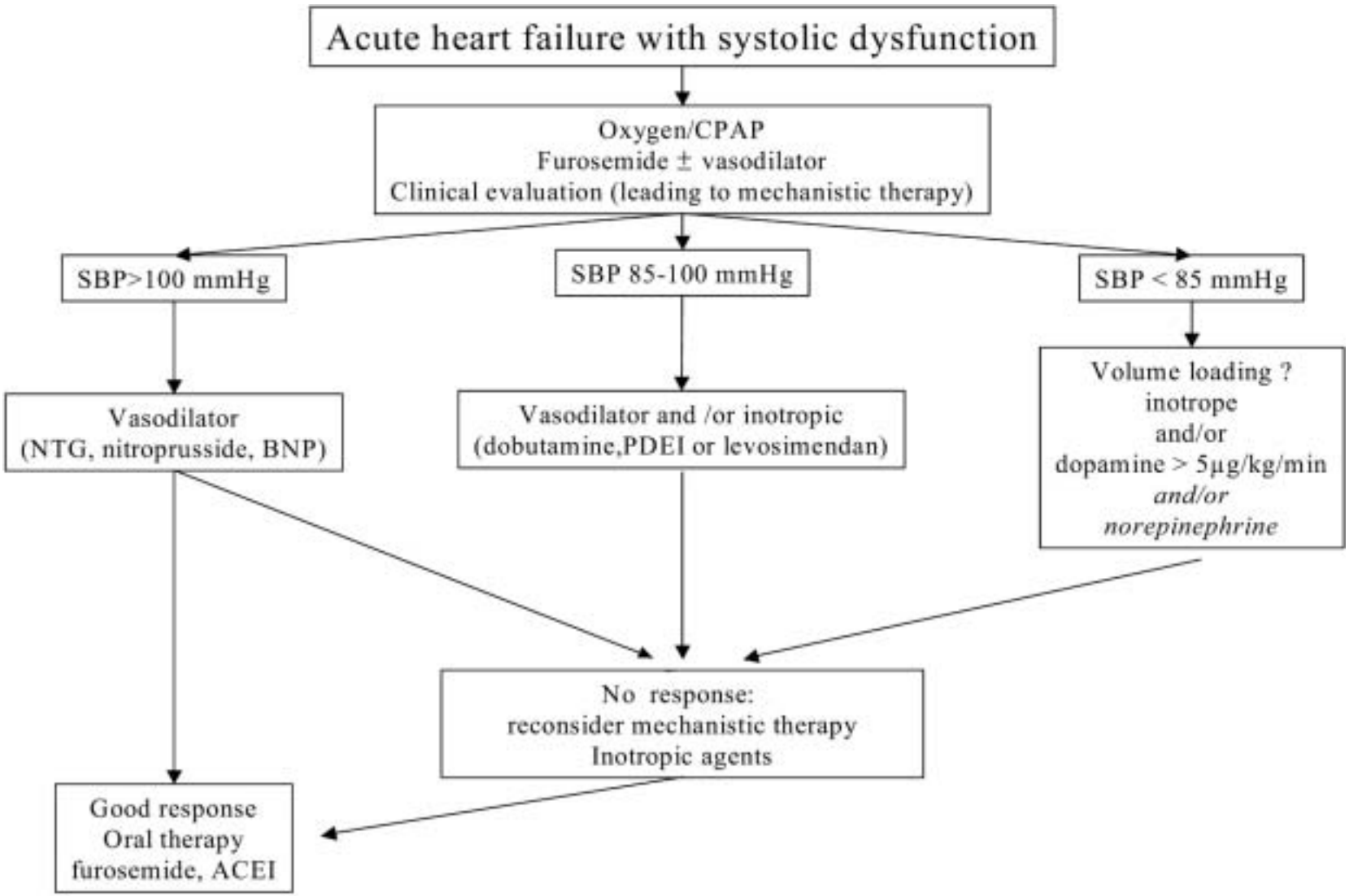
- Dopamine
  - 3 μ g/kg/min : increase renal blood flow
  - vasoconstriction in higher dose

Inotropics in ADHF

- Milrinone
  - phosphodiesterase inhibitor
  - increase sensitivity of beta stimulation

- Proarrhythmic effect

Rationale for inotropic drugs in ADHF



ESC guideline of acute heart failure, European heart journal 2005;26:384-416

Vasodilator in ADHF

- Nitroprusside

  - dramatically, decrease systemic vascular resistances (afterload)

  - usually, require invasive monitoring

  - titrate carefully, because of hypotension

  - consider coronary steal, pulmonary shunt

Vasodilator in ADHF

- Nitroglycerin
  - commonly used in acute ischemic syndrome
  - decreased preload and afterload
  - consider reflex sympathetic overactivity
- Nesiritide

Nesiritide (hBNP) Is Identical to the Endogenous Hormone

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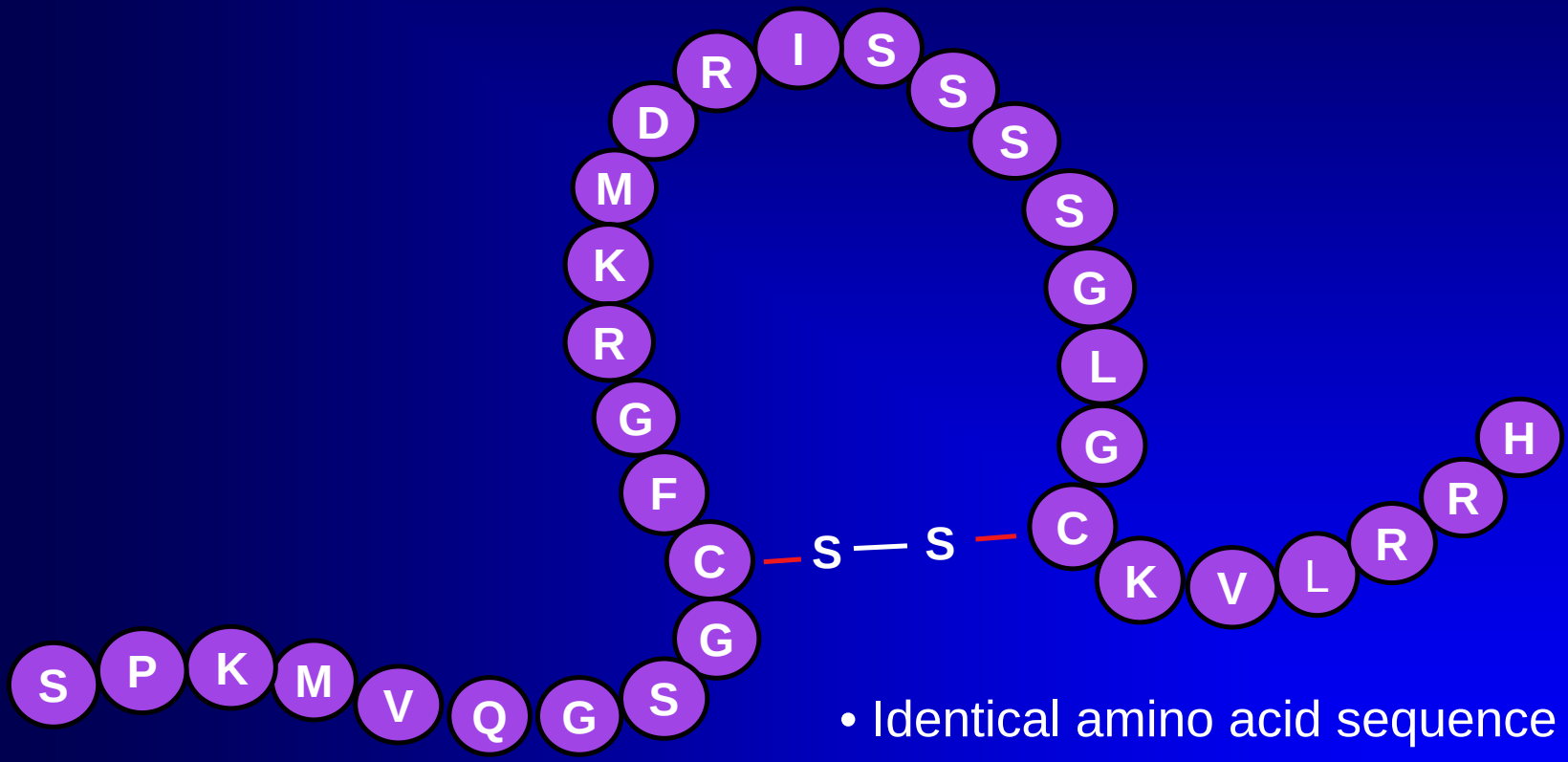
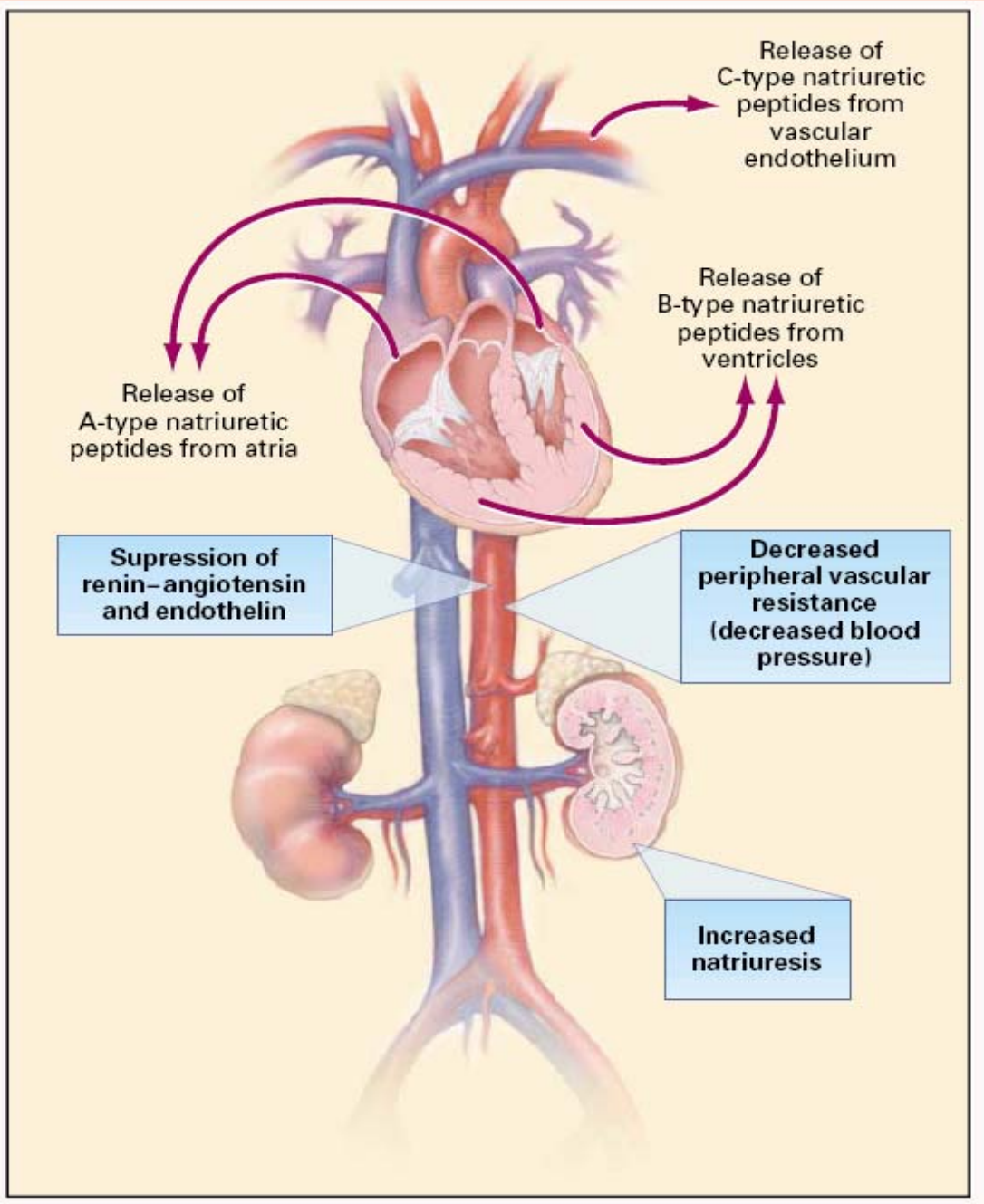


- Identical amino acid sequence
- Identical pharmacologic profile

Clemens LE et al. *J Pharmacol Exp Ther.* 1998;287:67–71.


Release of
C-type natriuretic
peptides from
vascular
endothelium
Release of
B-type natriuretic
peptides from
ventricles
Release of
A-type natriuretic
peptides from atria
Supression of
renin–angiotensin
and endothelin
Decreased
peripheral vascular
resistance
(decreased blood
pressure)
Increased
natriuresis

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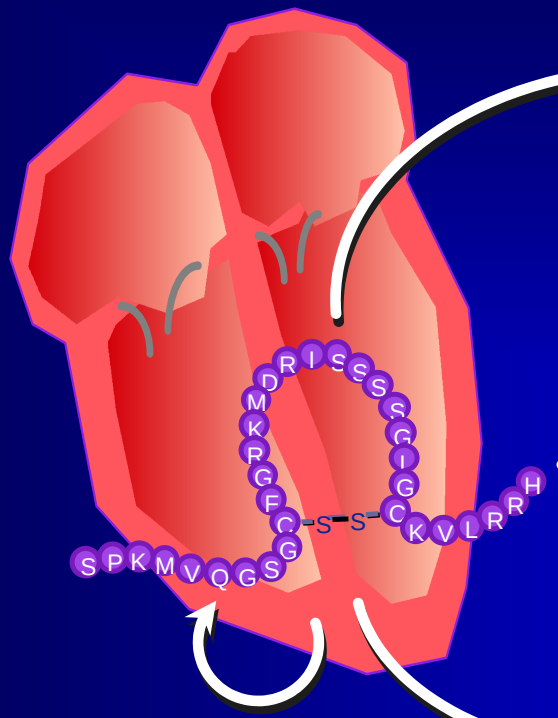
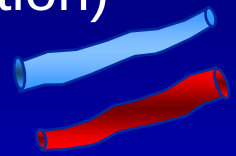
Pharmacologic Actions of hBNP



Hemodynamic[1,2]
(balanced vasodilation)

- veins
- arteries
- coronary arteries

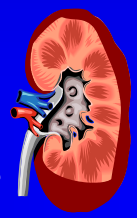


Neurohumoral[2]

- ↓ aldosterone[4]
- ↓ endothelin[2]
- ↓ norepinephrine[4]

Renal[1,5,6]

- ↑ diuresis
- ↑ natriuresis
- ↑ GFR



Cardiac [3]

- lusitropic
- antifibrotic
- anti-remodeling

1. Marcus LS et al. *Circulation.* 1996;94:3184–3189.
2. Zellner C et al. *Am J Physiol.* 1999;276(3 pt 2):H1049–H1057.
3. Tamura N et al. *Proc Natl Acad Sci U S A.* 2000;97:4239–4244.
4. Abraham WT et al. *J Card Fail.* 1998;4:37–44.
5. Clemens LE et al. *J Pharmacol Exp Ther.* 1998;287:67–71.
6. Rayburn BK, Bourge RC. Rev Cardiovasc Med. 2001;2(suppl 2):S25–S31

Hemodynamic Effects of Nesiritide in Heart Failure Patients

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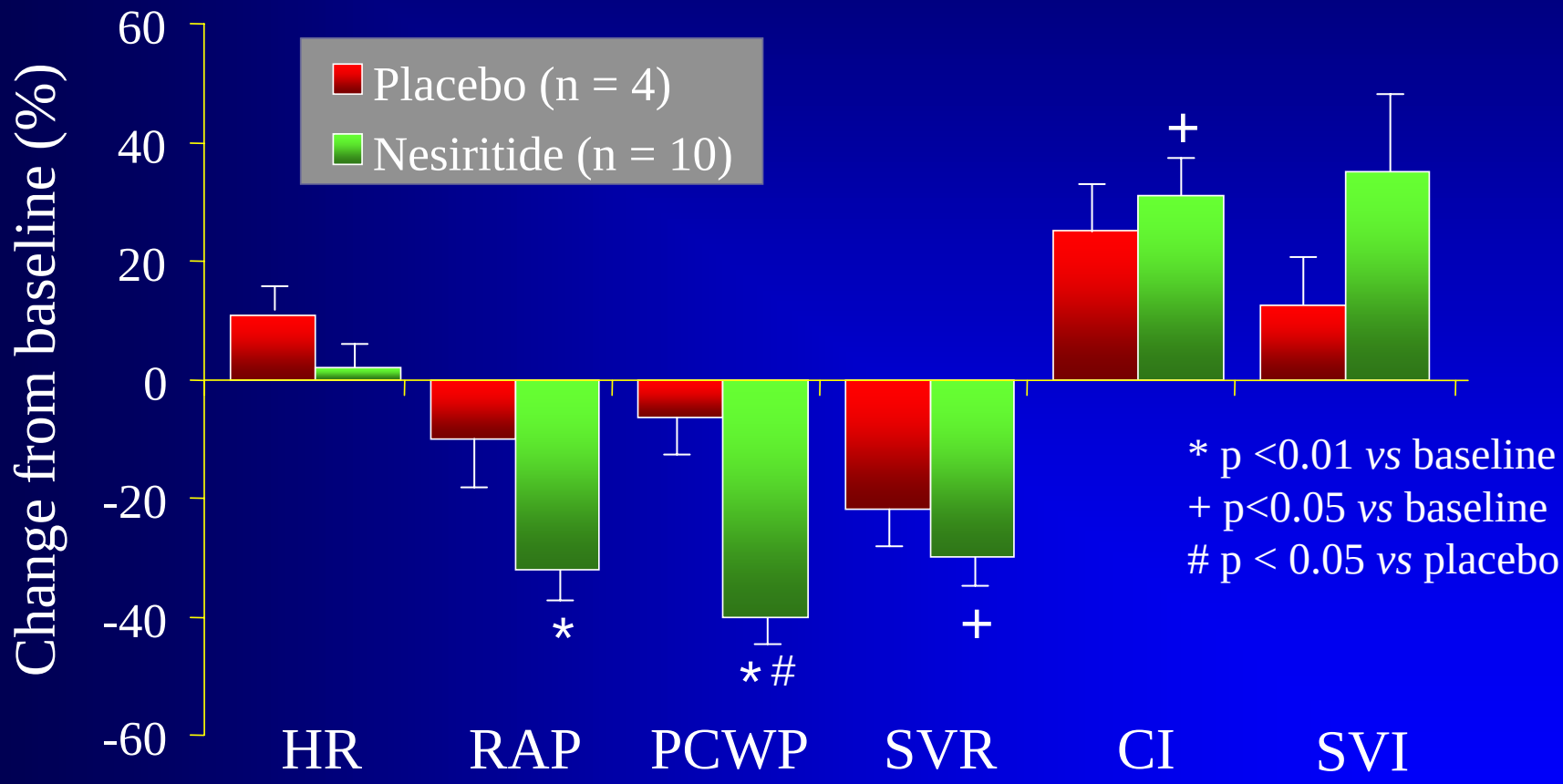
A Randomized, Double-Blind, Placebo-Controlled Trial



Abraham WT et al. *J Cardiac Failure* 1998;4:37-44

Effects of Natriuretic Peptides on the Kidney

- Dilatation of afferent and constriction of efferent renal arterioles, leading to pressure augmentation within the glomerular capillaries and, thus, to increased GFR[1]

- Relaxation of mesangial cells, which enhances effective surface area for filtration[2]

1. Rayburn BK, Bourge RC. *Rev Cardiovasc Med*. 2001;2(suppl 2):S25–S31.
2. Appel RG. *Am J Physiol*. 1990;251:F1036–F1042.

Effects of Natriuretic Peptides on the Kidney

- Inhibition of angiotensin II–stimulated sodium and water reabsorption in proximal convoluted tubules[1]
- Inhibition of tubular water transport by antagonizing effect of vasopressin[1]
- Decrease in plasma renin and aldosterone[2]

1. Appel RG. *Am J Physiol*. 1990;251:F1036–F1042.
2. Holmes SJ et al. *J Clin Endocrinol Metab.* 1993;76:91–96.

Nesiritide Efficacy Trial: Effects of Nesiritide on Urine Output[1] and Diuretic Use[2]

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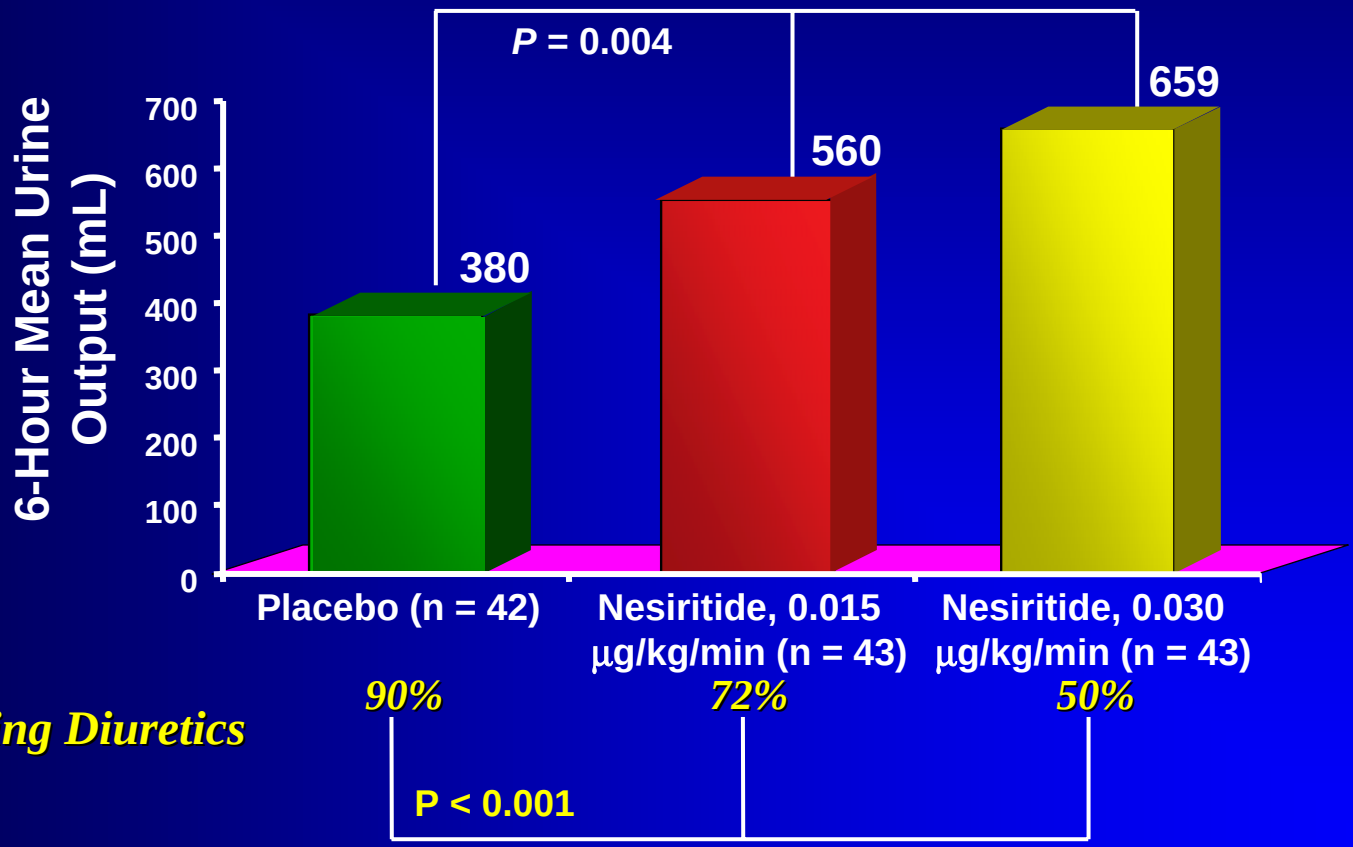

% Receiving Diuretics (24 h) [2].

1. Colucci WS et al. N Engl J Med. 2000;343:246–253.
2. Data on file. Scios Inc.

The Effects of Nesiritide on Neurohormones in CHF

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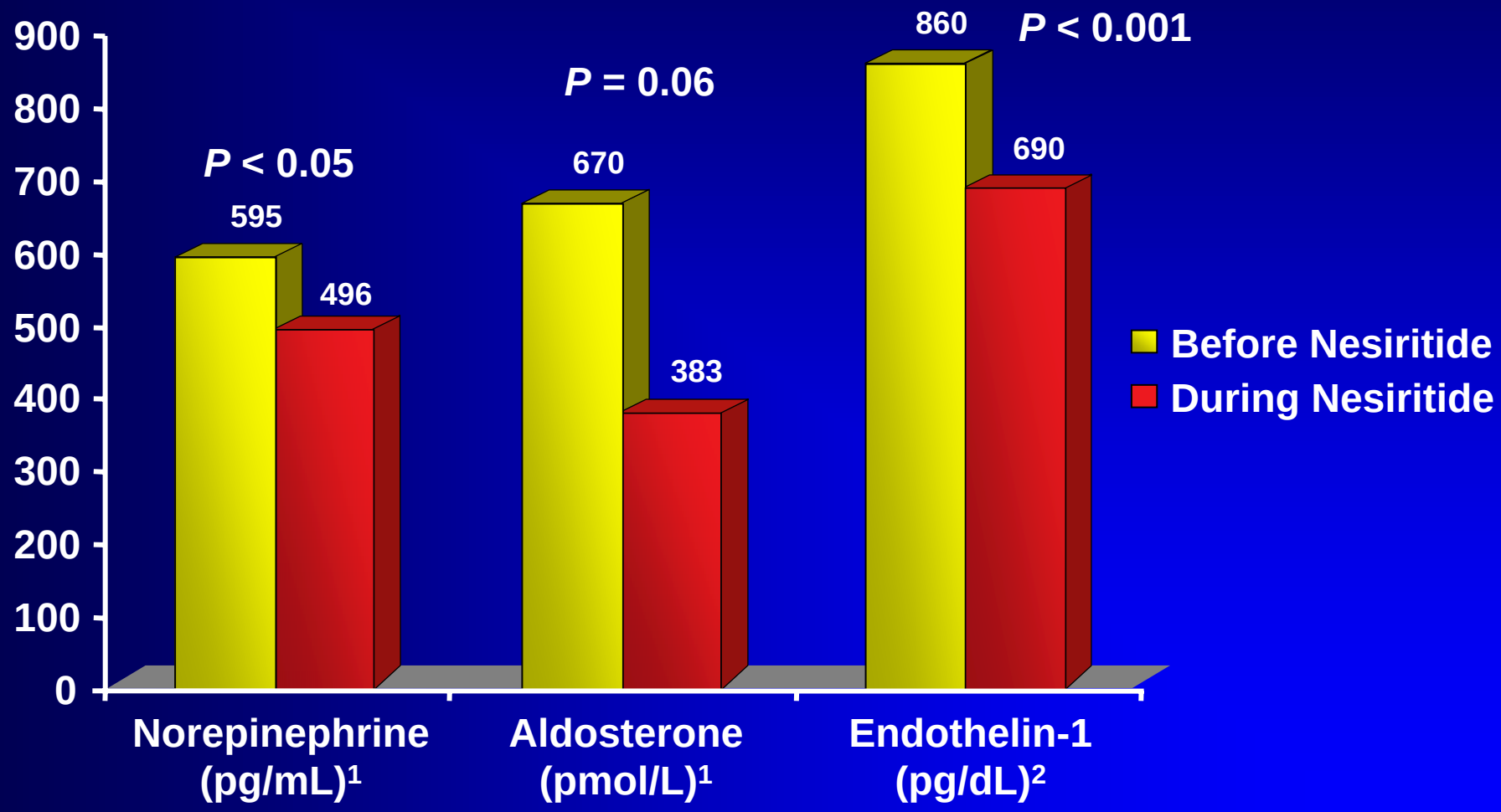
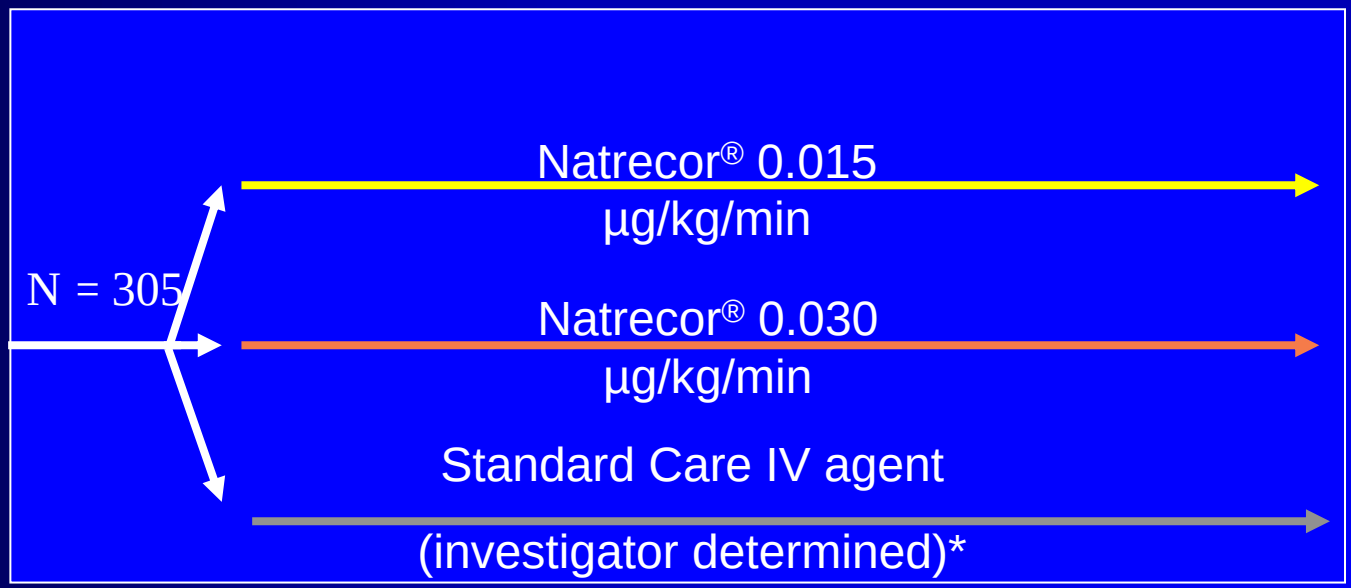


1. Abraham WT et al. J Card Fail. 1998;4:37–44.
2. Aronson D et al. J Am Coll Cardiol. 2001;37(2 suppl A):148A.

Comparative Trial

- Multicenter, randomized, active-controlled
- 305 subjects with decompensated CHF requiring IV vasoactive therapy
- Up to 7 days of Rx
- Central hemodynamic monitoring NOT required



*i.e. dobutamine, dopamine, milrinone, nitroglycerin, nitroprusside

Colucci WS, et al. *N Engl J Med* 2000;343:246-53

Comparative Trial: Duration of Treatment

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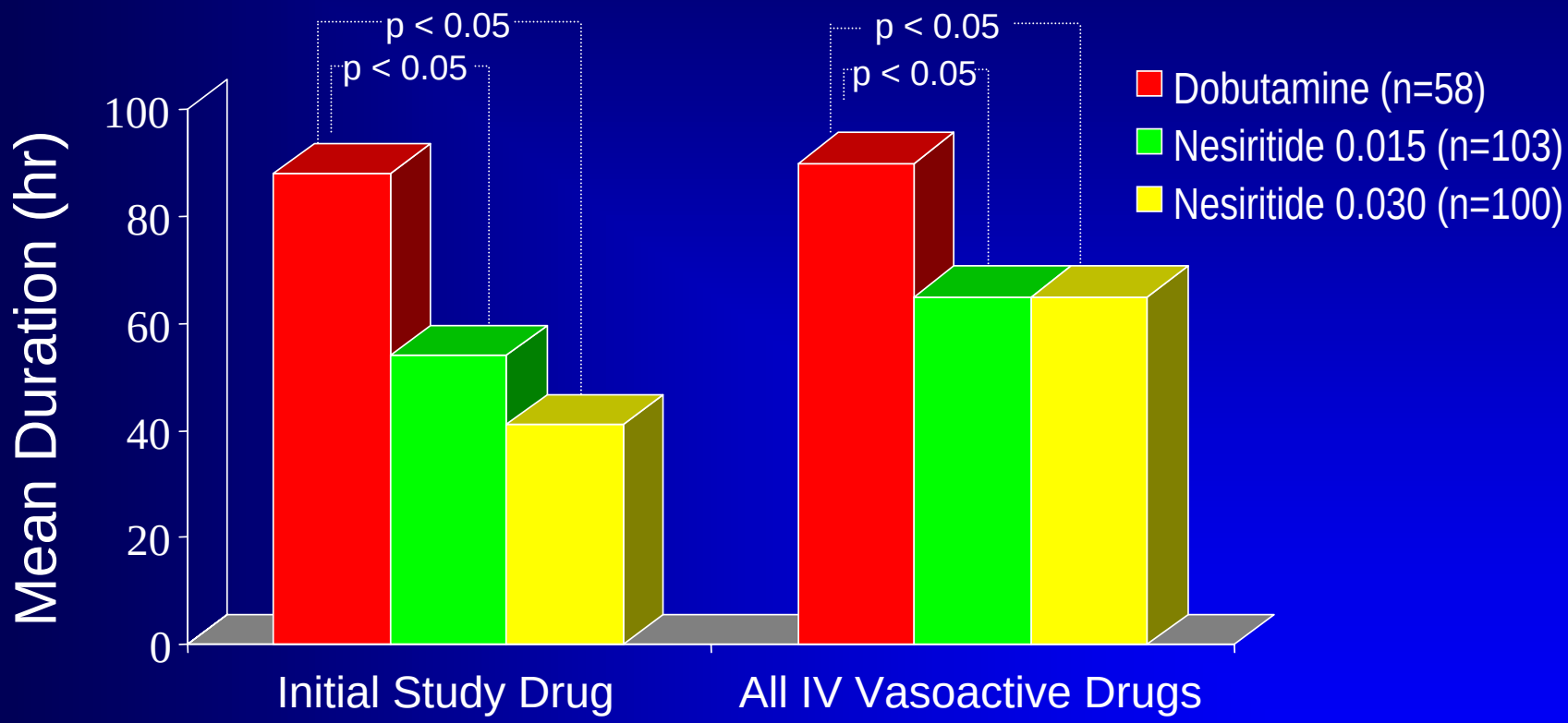

Silver MA. et al. *J Am Coll Cardiol* 2002; 39 (5): 798-803

Readmission Rates and Mortality Nesiritide Versus Dobutamine

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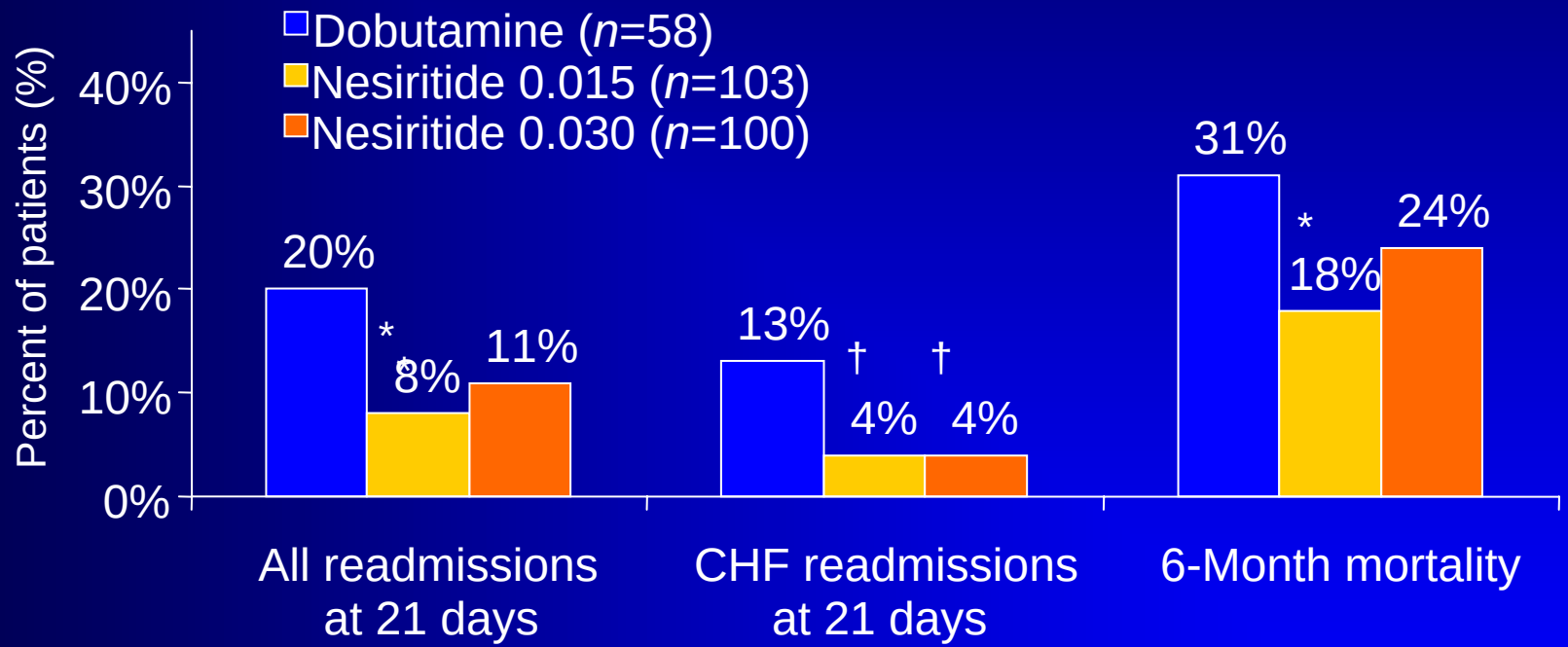

$p \leq 0.05$ vs. dobutamine

† $p < 0.06$ vs. dobutamine

Silver MA. et al. *J Am Coll Cardiol* 2002; 39 (5): 798-803

Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) Trial

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Design

- Phase III randomized, double-blind, placebo-controlled
- Multicenter (55) in the United States
- Randomization strategy based on **right-sided heart catheterization**
- 489 patients enrolled from October 1999 to July 2000
- Acutely decompensated heart failure with dyspnea on admission
- Nesiritide vs IV nitroglycerin vs placebo when added to standard therapy
  - fixed-dose IV nesiritide
  - variable-dose IV nesiritide
  - IV nitroglycerin
  - placebo

VMAC Investigators. JAMA. 2002;187:1531–1540.

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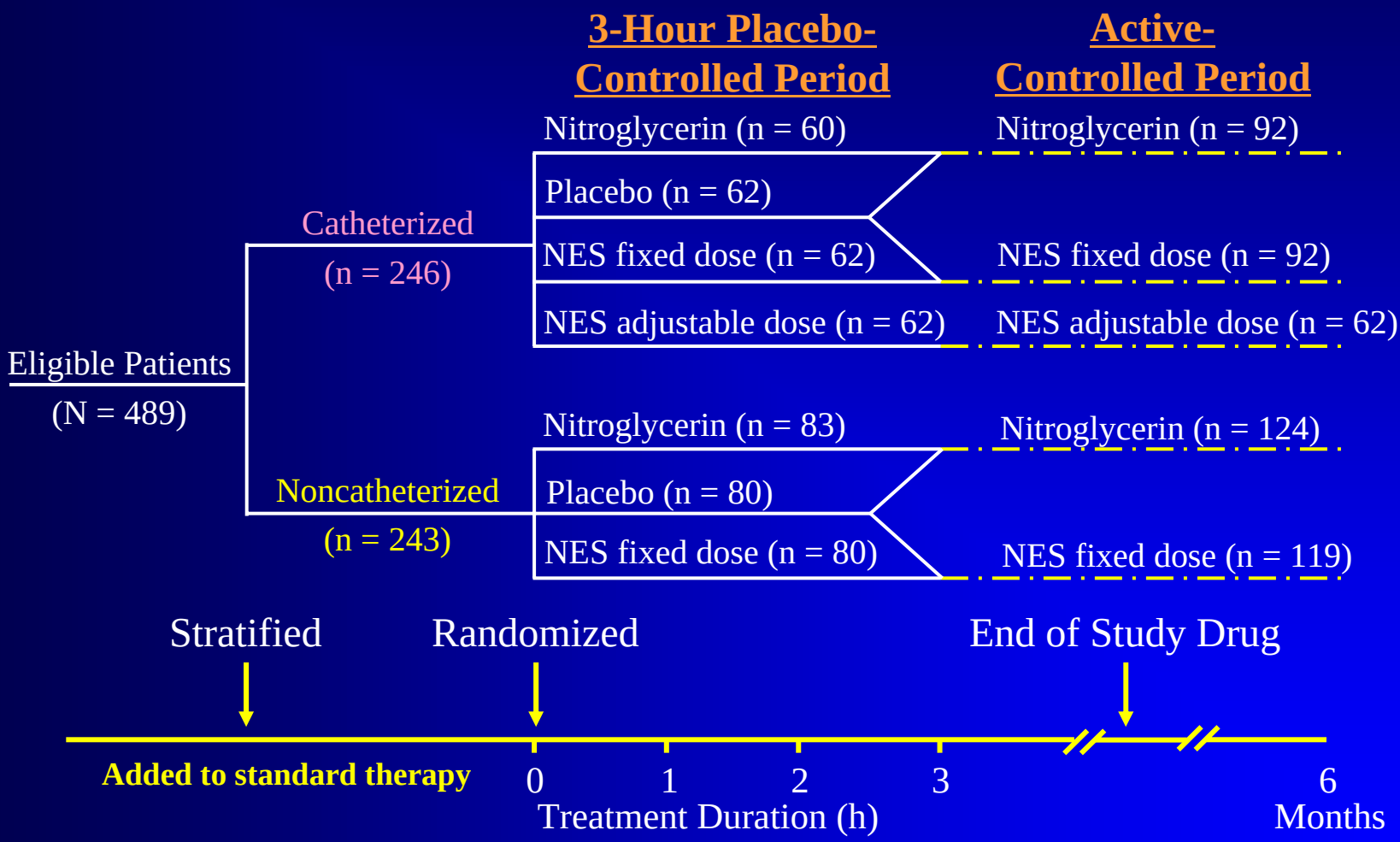
VMAC: Study Design



Scios Inc. NDA 20-920 Cardiovascular and Renal Drugs Advisory Committee Briefing Document: Natrecor (nesiritide) for Injection. Sunnyvale, CA: Scios Inc; May 25, 2001.

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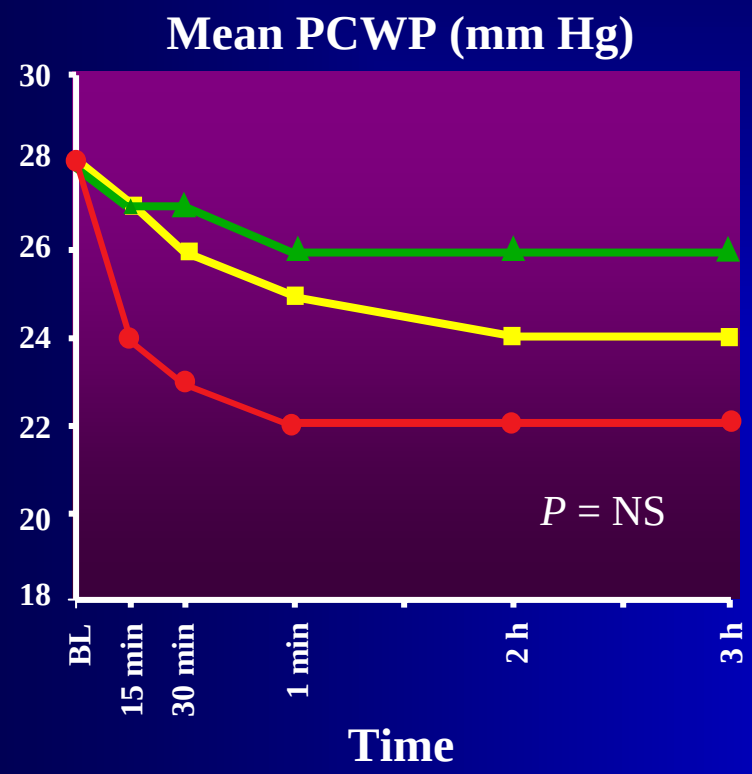
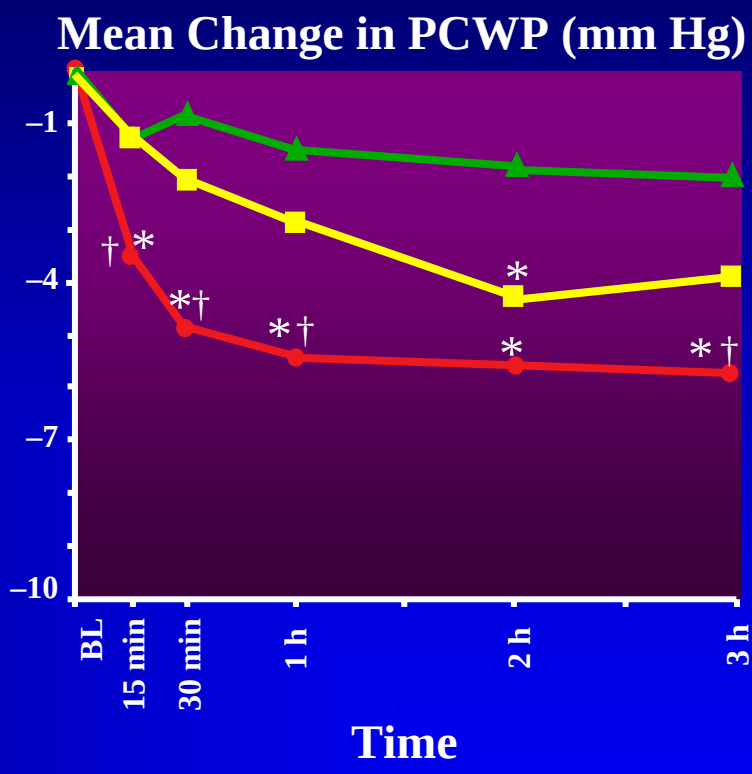
VMAC: PCWP Through 3 Hours



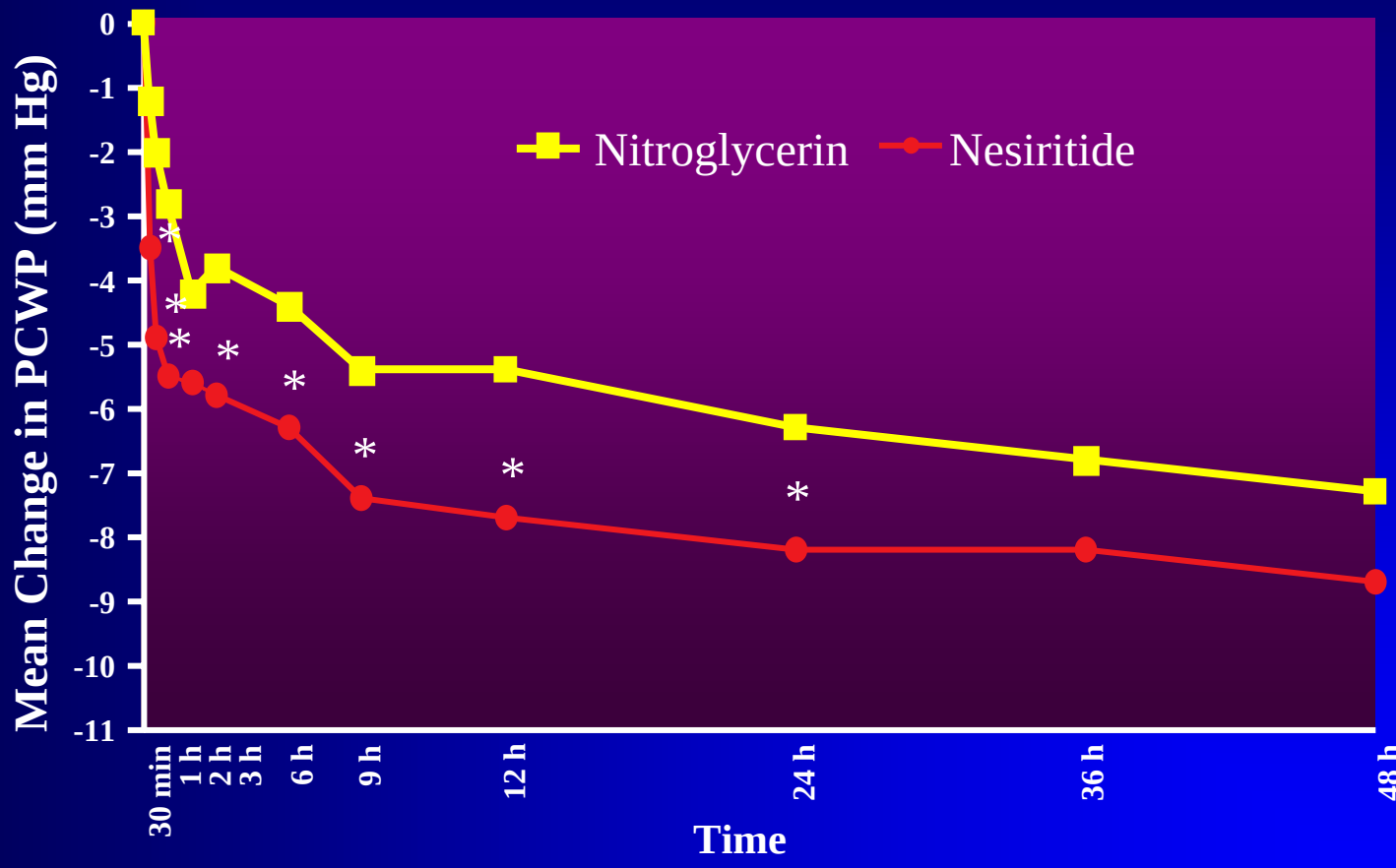


*$P < 0.05$ vs placebo.
†$P < 0.05$ vs nitroglycerin.

▲ Placebo ■ Nitroglycerin ● Nesiritide

VMAC Investigators. JAMA. 2002;187:1531–1540.

VMAC: PCWP Through 48 Hours



*$P < 0.05$ pooled nesiritide vs nitroglycerin.

VMAC Investigators. JAMA. 2002;187:1531–1540.

Nesiritide: Greater Pulmonary Vasodilation Than Nitroglycerin

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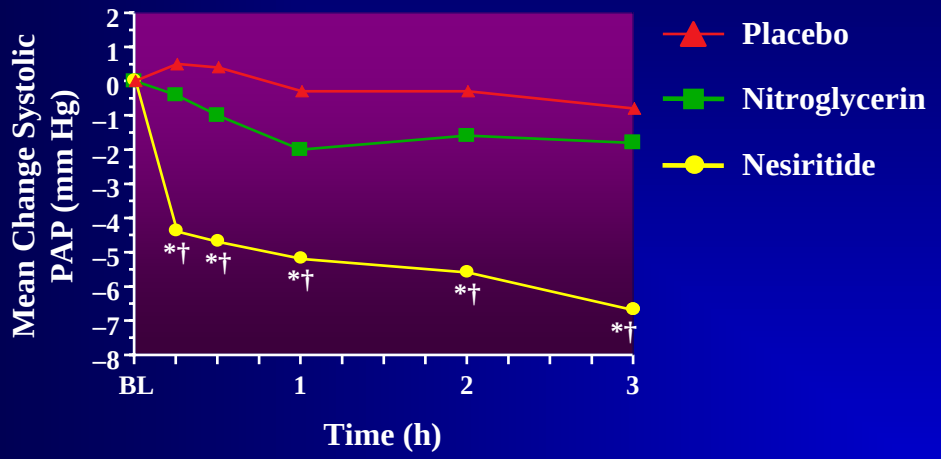

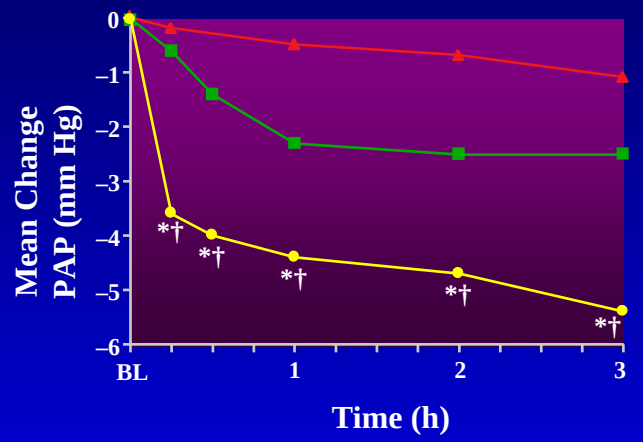

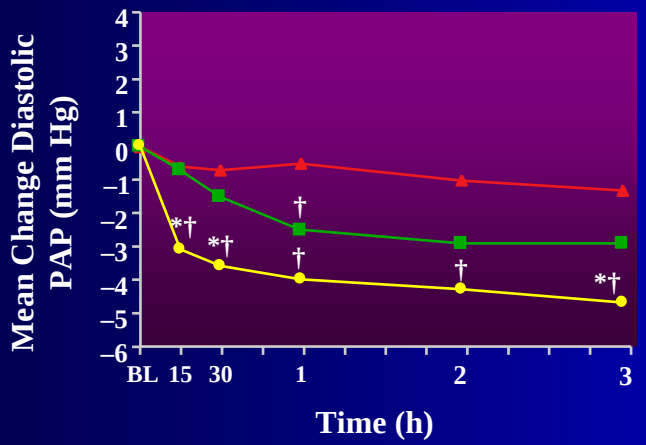

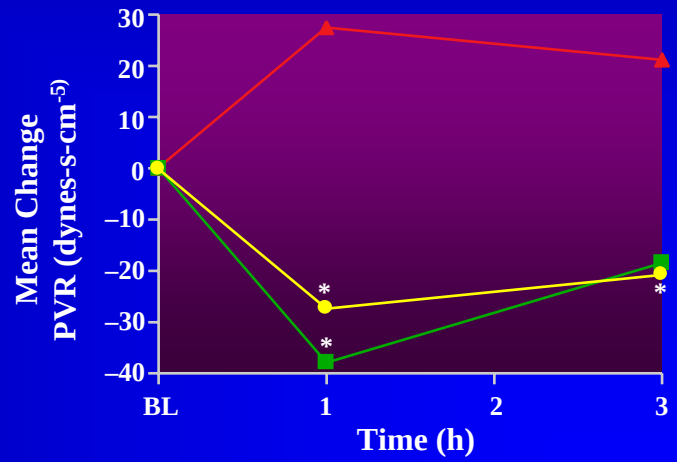

*$P < 0.05$ vs placebo; †$P < 0.05$ vs nitroglycerin.

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

VMAC Investigators. JAMA. 2002;187:1531–1540

Nesiritide Efficacy: Dyspnea Improvement in VMAC Trial

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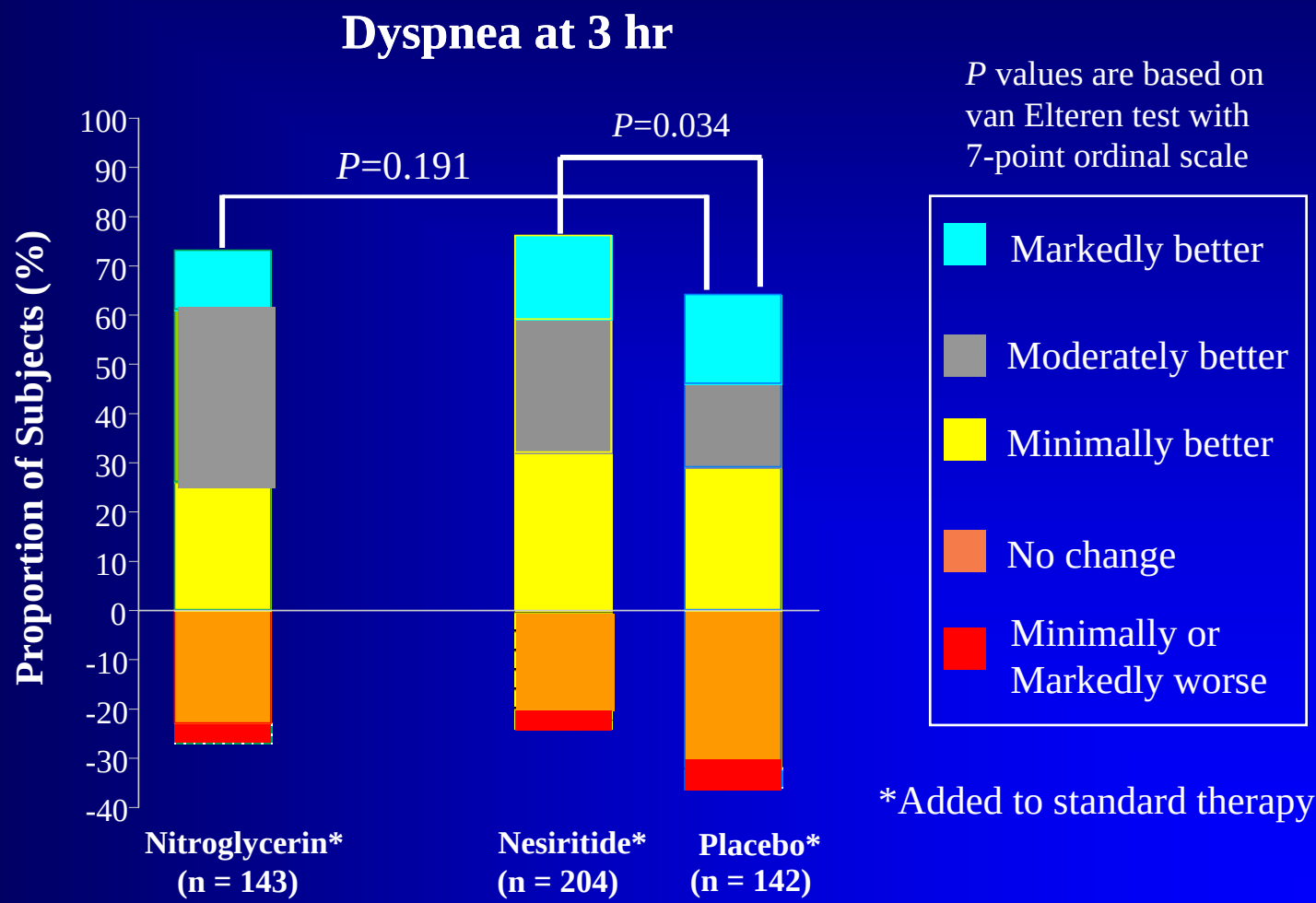

Publication Committee for the VMAC Investigators. *JAMA*.2002;287:1531

VMAC: Kaplan-Meier Estimate of Mortality Rate by Treatment Group

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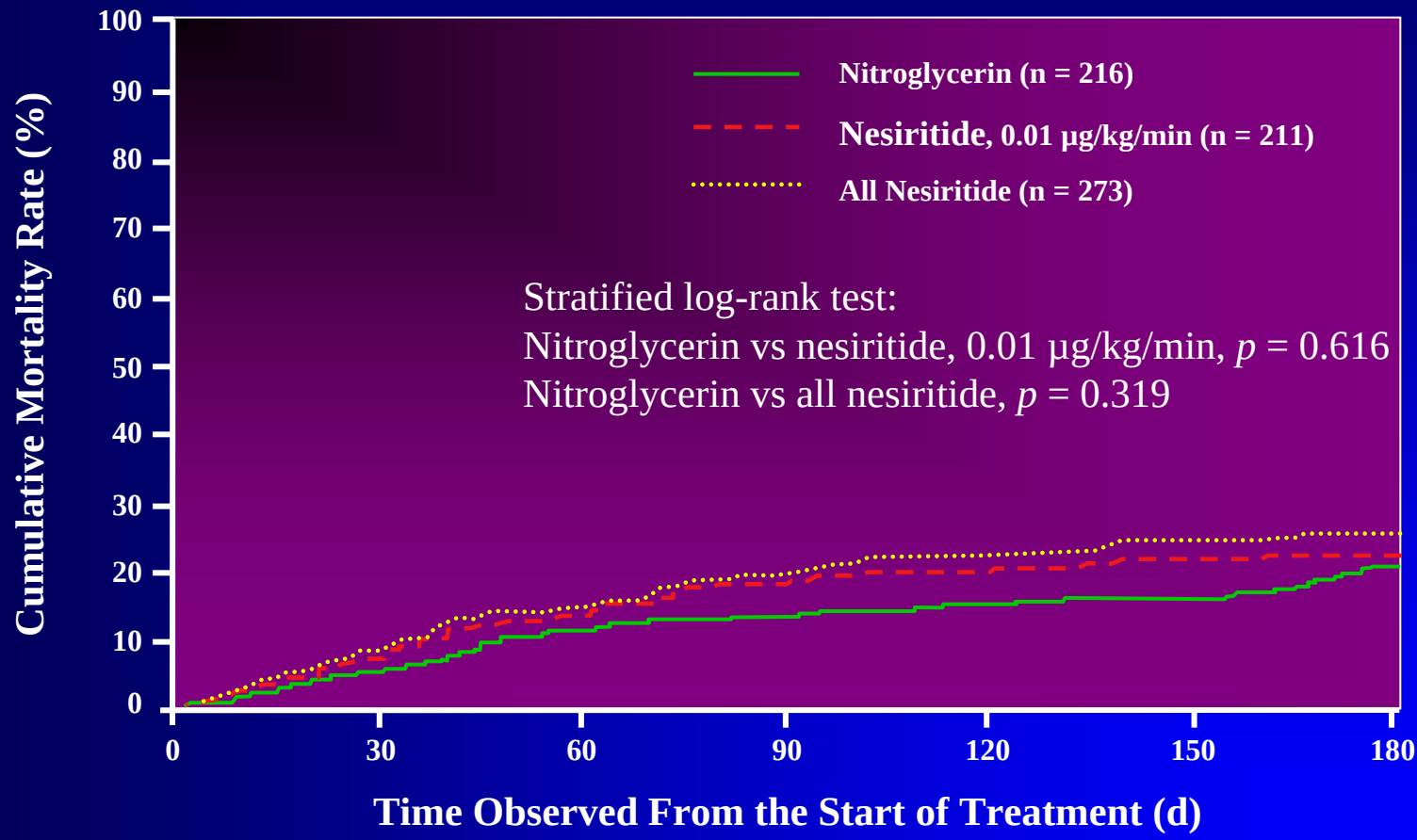

Scios Inc. NDA 20–920 Cardiovascular and Renal Drugs Advisory Committee Briefing Document: Natrecor (nesiritide) for Injection. Sunnyvale, CA: Scios Inc; May 25, 2001.

VMAC: Relationship Between Decrease in PCWP and Decrease in SBP With Vasodilation

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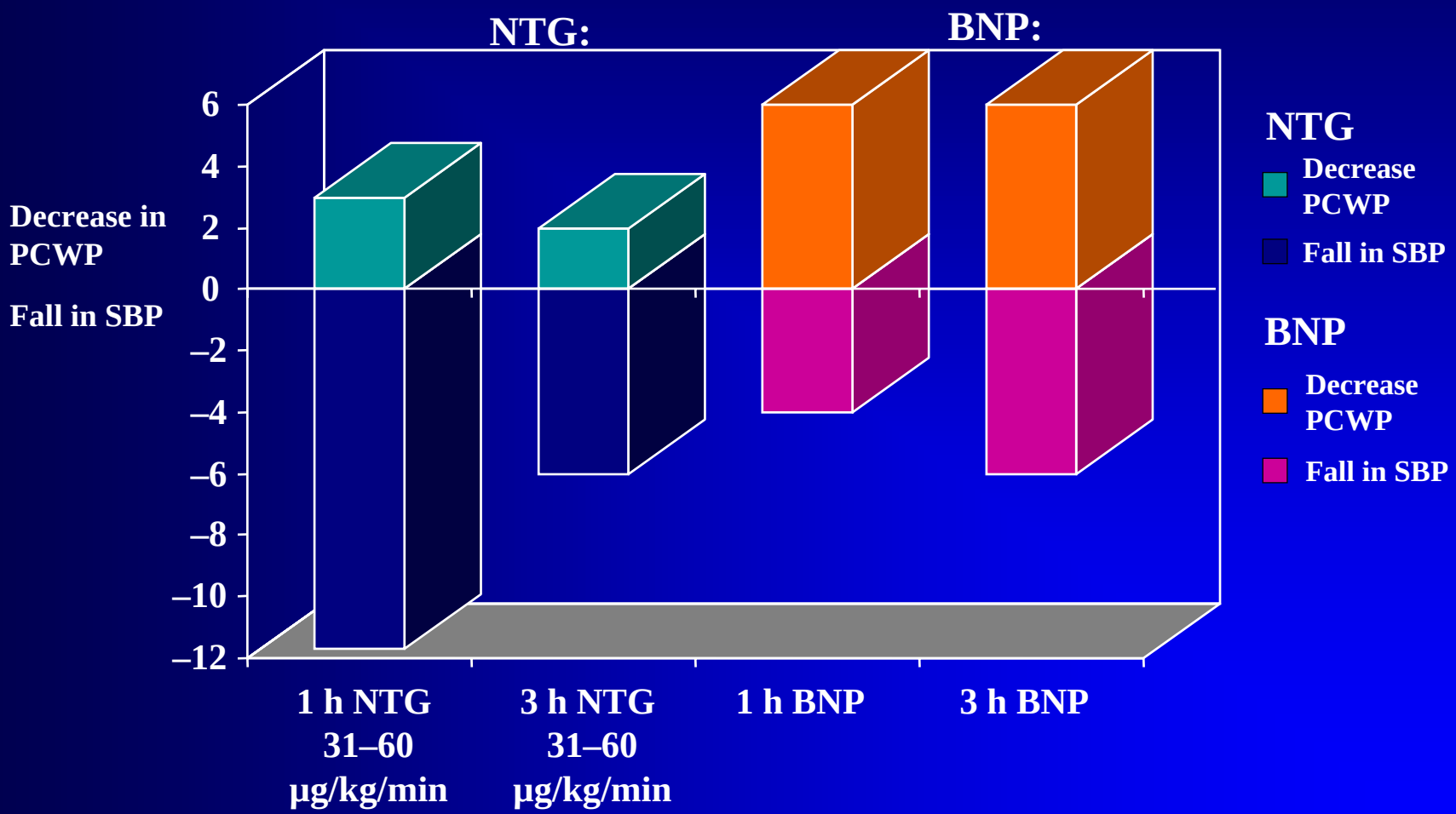

Stevenson LW on behalf of the VMAC Study Group.
Presented at: HFSA 5th Annual Scientific Meeting 2001; September 9–12, 2001; Washington, DC.

VMAC: Nesiritide Safety versus IV NTG adverse Events (First 24 Hours)

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	Nitroglycerin (n=216)	Natrecor (n=273)	p-value [1]
Any Adverse Event	**146 (68%)**	140 (51%)	<0.001
Headache	**44 (20%)**	21 (8%)	<0.001
Abdominal Pain	**11 (5%)**	4 (1%)	0.032
Symptomatic Hypotension	10 (5%)	12 (4%)	1.000
Ventricular Tachycardia	11 (5%)	9 (3%)	0.362
Angina Pectoris	5 (2%)	5 (2%)	0.756
Nausea	13 (6%)	10 (4%)	0.283
Dizziness	4 (2%)	7 (3%)	0.762

[1] Fisher's Test

Publication Committee for the VMAC Investigators. *JAMA* 2002; 287(12): 1531 -40

Lack of Ischemic Cardiovascular Adverse Events in VMAC

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Adverse Events 24 Hours After Start of Study Drug

	Nitroglycerin (n = 216)	All Nesiritide (n = 273)
Symptomatic hypotension	10 (5%)	12 (4%)
Ventricular tachycardia	11 (5%)	9 (3%)
Myocardial infarction	3 (1.4%)	2 (0.7%)
Angina	5 (2%)	5 (2%)

p = not significant.

VMAC Investigators. *JAMA*. 2002;187:1531–1540.

VMAC: Clinical Implications

- Nesiritide rapidly reduced PCWP and relieved symptoms in patients with acute heart failure more effectively than standard care alone and standard care plus IV nitroglycerin

- Nesiritide was as safe as and better tolerated than IV nitroglycerin

VMAC Investigators. *JAMA*. 2002;187:1531–1540.

Nesiritide vs Dobutamine: Clinical Effects and Proarrhythmic Potential

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PRECEDENT Trial

- Randomized, controlled
- Parallel arm
  - Dobutamine ≥ 5 μg/kg/min
  - Nesiritide, 0.015 μg/kg/min
  - Nesiritide, 0.030 μg/kg/min
- N = 255
- Acutely decompensated CHF
  - NYHA class III or IV
- 24-h baseline Holter
- 24-h Holter during treatment

Burger AJ et al. *Am Heart J.* 2002;144:1102–1108.

Effect of Short-Term Nesiritide vs Dobutamine on 6-Month Survival

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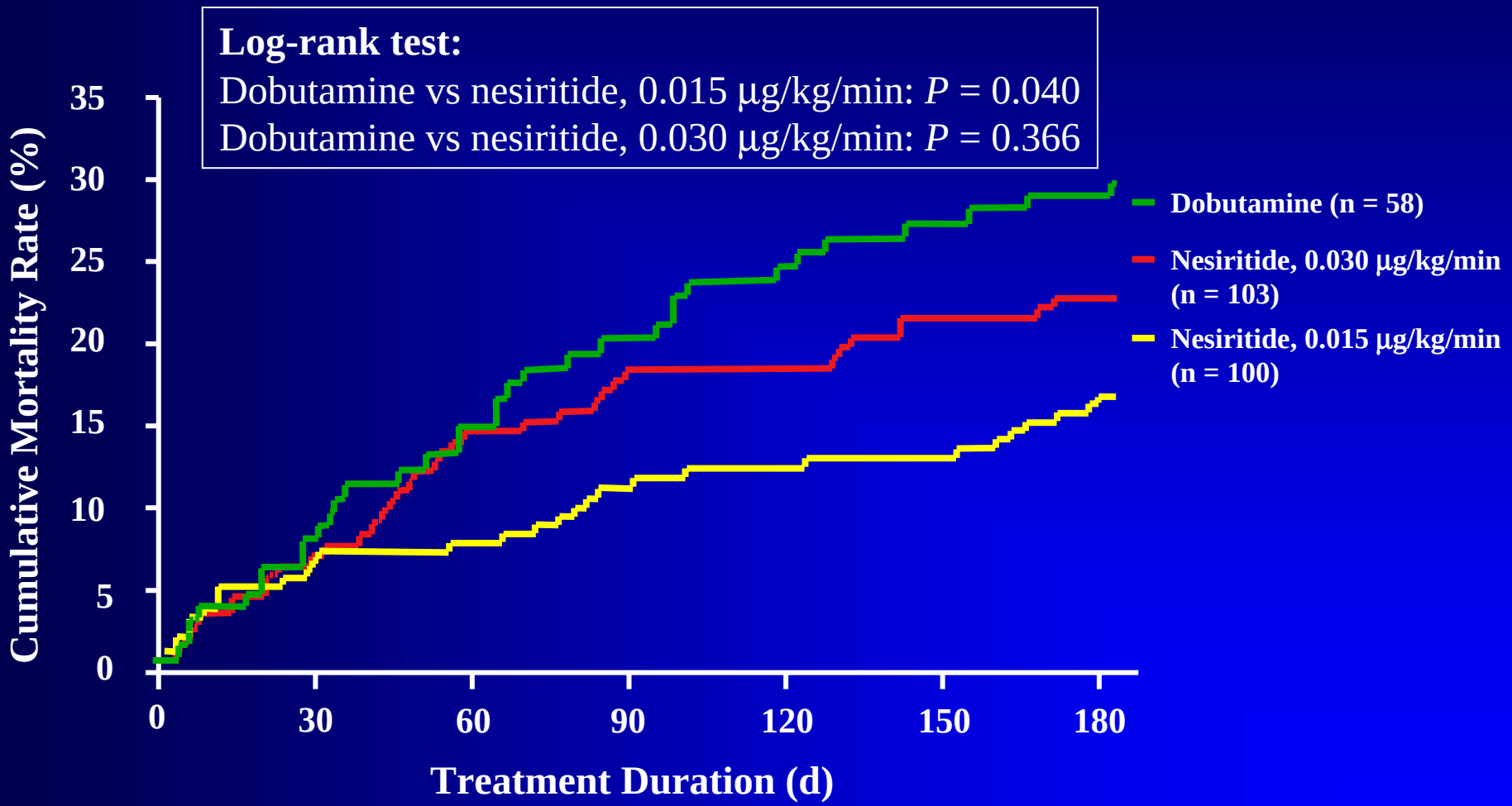

Silver MA et al. *J Am Coll Cardiol*. 2002;39:798–803.

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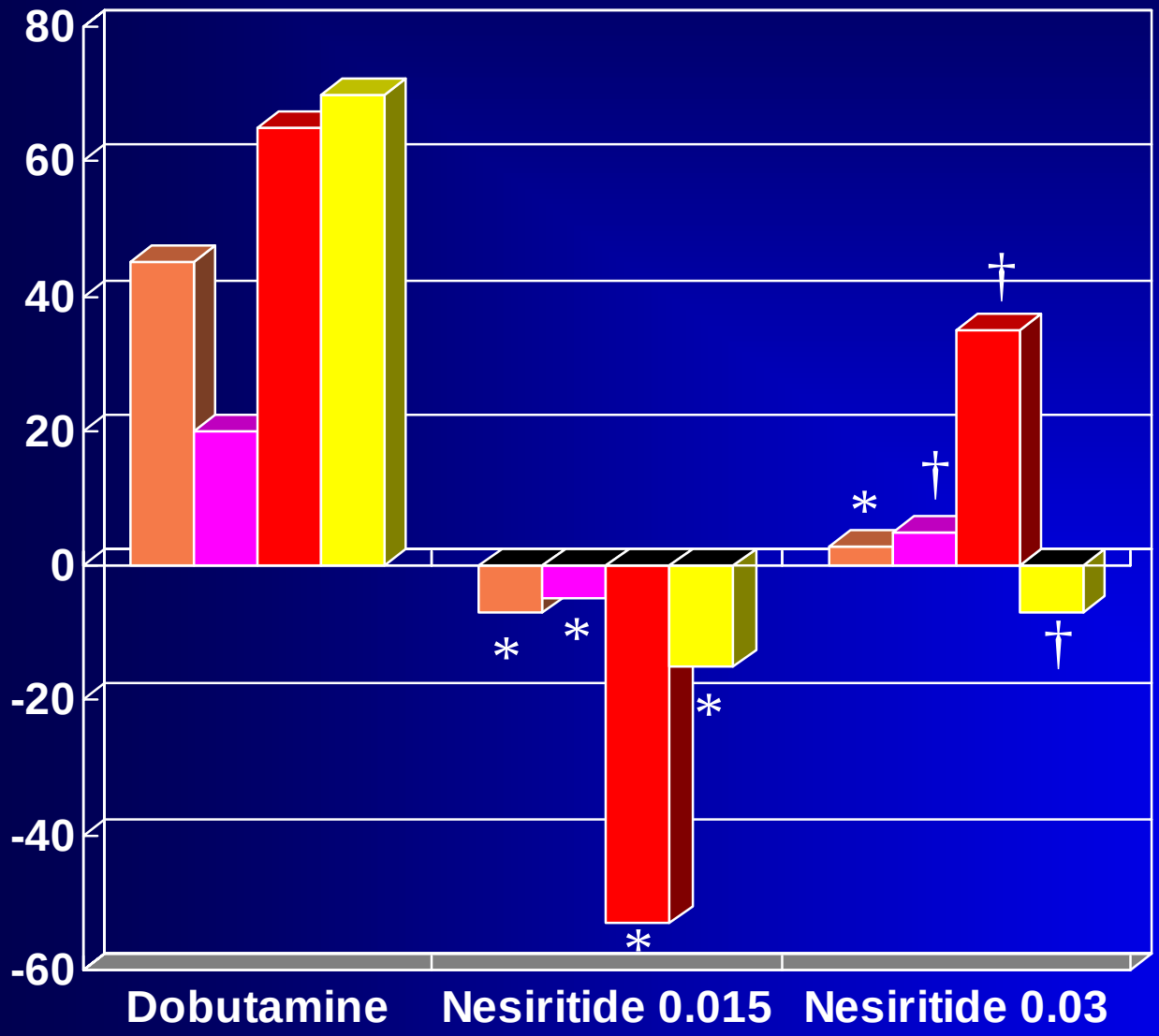
Arrhytmia between Nesiritide and Dobutamine



* : p<0.001 (vs dobutamine)

† : p<0.05 (vs dobutamine)

PRECEDENT : Clinical Implications

- Nesiritide had no proarrhythmic effects, whereas dobutamine was associated with an increased risk of SVT and cardiac arrest

- Nesiritide use resulted in shorter duration of IV medications and lower rate of re-hospitalization

Silver MA et al. *J Am Coll Cardiol.* 2002;39:798–803.

PRECEDENT : Clinical Implications

- Nesiritide, 0.015 µg/kg/min, was associated with improved 6-month survival compared with in-hospital use of dobutamine

Silver MA et al. *J Am Coll Cardiol.* 2002;39:798–803.

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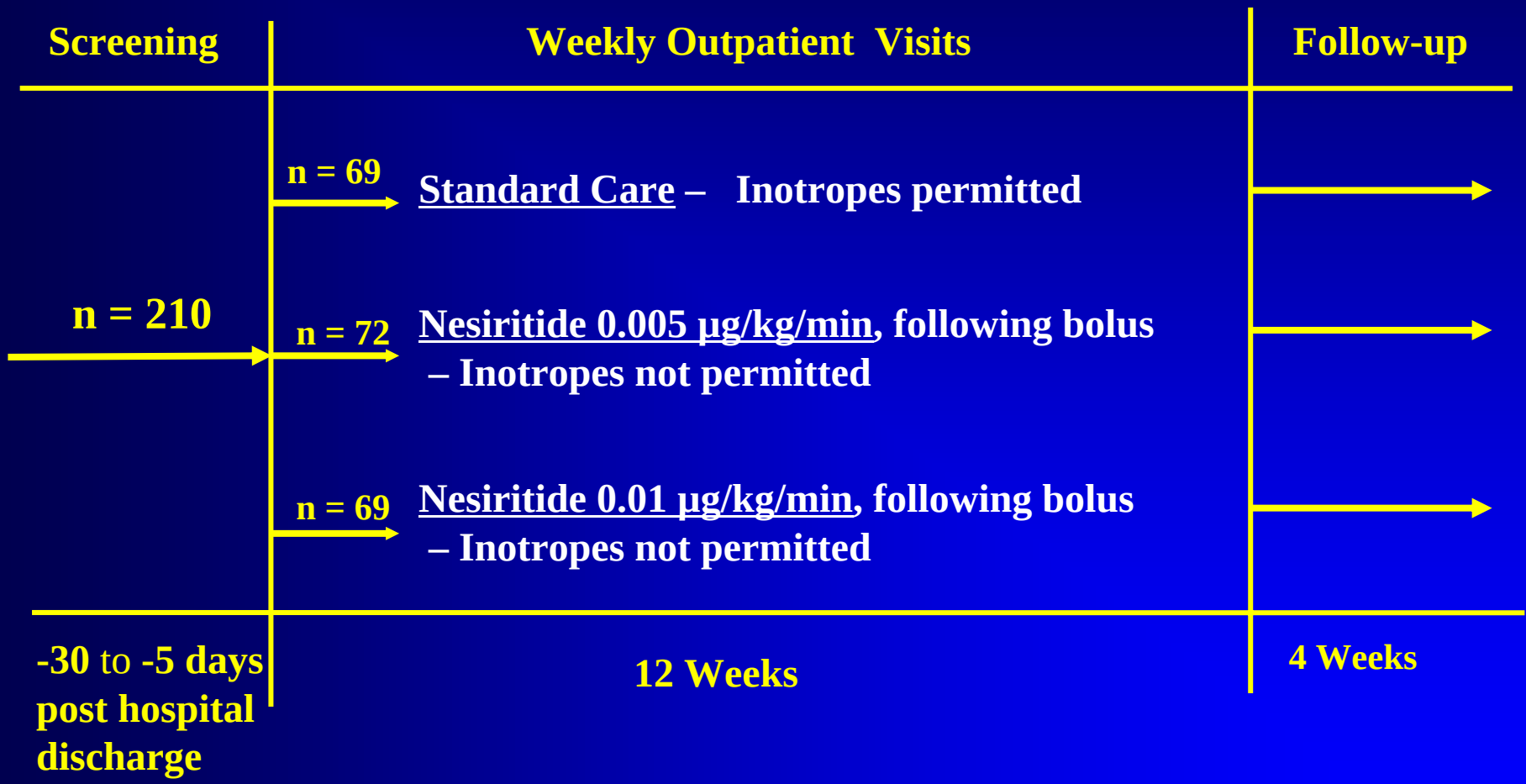
FUSION Study Design



Yancy CW et al. *Am J Cardiol.* 2004;94(5):595-601

Reasons for Study Drug Termination

	Nesiritide 0.005 (n = 72)	Nesiritide 0.01 (n = 69)	All Nesiritide (n = 141)
Infusions with Termination Due to:			
Normal Termination	814 (99%)	814 (99%)	1628 (99%)
Adverse Event	4 (<1%)	7 (1%)	11 (1%)
Patients with Termination Due to:			
Adverse Event	4 (6%)	5 (7%)	9 (6%)

Yancy CW et al. *Am J Cardiol.* 2004; 94: 595-601

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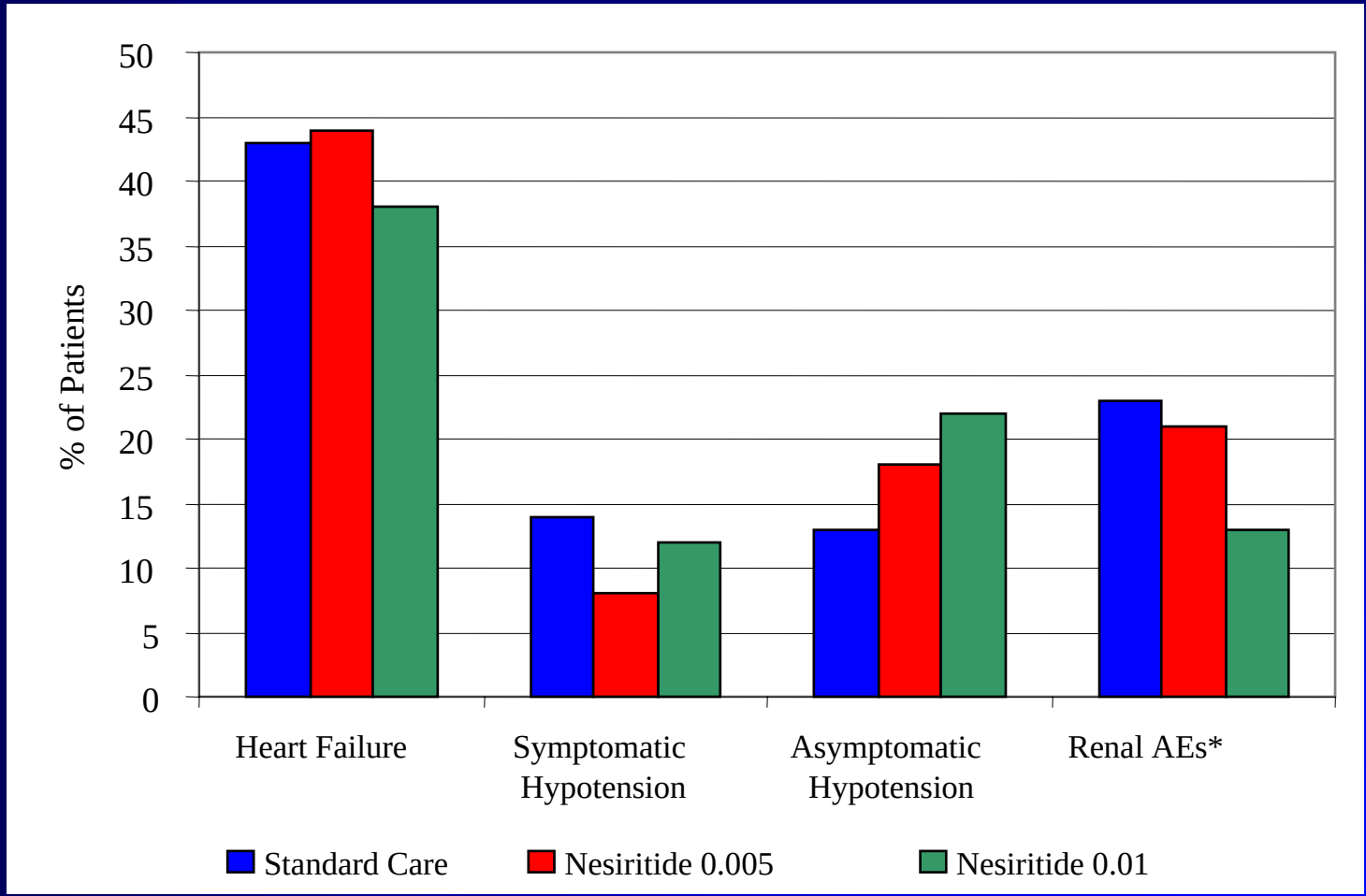
Selected AE's – All Patients



*Renal AEs include:

BUN increased, abnormal kidney function, acute kidney failure, increased creatinine, and oliguria

Clinical Outcomes Through Week 12 – All Patients

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Clinical Outcome	Standard Care (n = 69)	Nesiritide 0.005 Dose (n = 72)	Nesiritide 0.01 Dose (n = 69)	All Nesiritide Patients (n = 141)
Patients alive and never hospitalized	29 (42%)	39 (54%)	35 (51%)	74 (52%)
Deaths	7 (10%)	6 (8%)	3 (4%)	9 (6%)
All cause hospitalization	37 (54%)	32 (44%)	33 (48%)	65 (46%)
Days alive and out of hospital				
Mean ± SD	74 ±18	76 ± 15	79 ± 11	78 ± 13
25th percentile	73.8	74.2	79.0	77.6

Yancy CW et al. *Am J Cardiol.* 2004; 94: 595-601

Improvement in Left Ventricular Systolic Function

	Standard Care (n=38)	Nesiritide 0.005 Dose (n=40)	Nesiritide 0.01 Dose (n=37)	All Patients (n=77)
EF at Baseline	29.6 +/- 18.6	28.8 +/- 15.8	27.7 +/- 13.8	28.25 +/- 14.8
Change at 12 weeks	3.2 +/- 3.8	4.0 +/- 3.3	5.3 +/- 5.0	4.6 +/- 4.2
P value*	N/A	0.44	0.03	0.09

*Compared to standard care.

Nesiritide: Overall Clinical Profile

- Vasodilation (venous > arterial)[1]
- Rapidly improves symptoms of congestion[1]
- Does not increase heart rate (decreases myocardial oxygen demand)[1]
- Is not proarrhythmic[1]

1. Fonarow GC. *Rev Cardiovasc Med*. 2001;2(suppl 2):S32–S35.

Nesiritide: Overall Clinical Profile

- Neurohormonal suppression (decreases aldosterone, NE)[1]
- Mild diuresis / natriuresis[2]
- No evidence of tachyphylaxis[3]
- Symptomatic hypotension as low as 4% in VMAC[1]
- Dosing convenience (bolus + standard-dose IV infusion)[3]

1. Fonarow GC. *Rev Cardiovasc Med.* 2001;2(suppl 2):S32–S35.
2. Rayburn BK, Bourge RC. *Rev Cardiovasc Med.* 2001;2(suppl 2):S25–S31.
3. Natrecor (nesiritide) [package insert]. Sunnyvale, CA: Scios Inc; 2001.

Role of Nesiritide : Summary

- First, used in addition to diuretics and before conventional vasodilators and inotropes
- Excellent benefit / risk profile;
  hypotension is the major side effect
- Avoid in patients with cardiogenic shock, systolic blood pressure <90 mm Hg, or in patients with low cardiac filling pressures

Role of Nesiritide : Summary

- Can be used in patients with renal disease, acute coronary syndromes, diastolic dysfunction, and with serious arrhythmias
- Initial bolus dose (2 mcg/kg) followed by a fixed-dose infusion (0.01 mcg/kg/min)
- may increase infusion rate of nesiritide up to a maximum of 0.03 μg/kg/min

Expanding the Therapeutic Applications of Natriuretic Peptides

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Efficacy Trial, VMAC, PROACTION, PRECEDENT, FUSION I

↓ **Dyspnea & PCWP in ADHF**

Over 1,400 patients

Ongoing or Pending Investigations

FUSION II	NAPA	TMAC	EMAC	PMAC	REMAC	CMAC
Serial Outpatient Infusion	Peri-Post CT Surgery Administration	Continuous Infusion Prior to heart **Transplantation**	Continuous Outpatient Infusion **End-Stage HF**	Early ED Administration in aHF w/ **Pulmonary**	Early Administration aHF worsening **Renal** function	Early ED + Cath Administration in **ACS**

Future Possibilities

CKD | PAH | Surgery | PEDS | Diastolic HF