VASODILATADORES NA INSUFICIÊNCIA CARDÍACA AGUDA - O ETERNO DESAFIO

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Centro Hospitalar Lisboa Norte, EPE

AHF – definition

Is the term used to describe the rapid onset, or changing, symptoms and signs of HF.

It is a life threatening condition that requires immediate medical attention

In most cases, AHF arises as a result of deterioration in patients with previous diagnostic of HF. In these patients there is often a clear precipitant or trigger.

AHF – definition ???

AHF IS NOT A SINGLE DISEASE, BUT RATHER A HETEROGENEOUS FAMILY OF CLINICAL SYNDROMES, EACH WITH DISTINCT CLINICAL PRESENTATION, PROGNOSIS AND MANAGEMENT

CHARACTERISTICS OF PATIENTS WITH DE NOVO HF AND ADCHF: EUROHF-II

Variable, % of pts.	ADCHF (n=2251)	De novo HF (n=1235)	P value
Males	64	57	<0.001
Renal failure	20	11	<0.001
Dilated cardiomyopathy	25	9.5	<0.001
History of CHD	62	39	<0.001
Acute coronary syndrome	23	42	<0.001
STEMI	6	20	<0.001
NSTEMI	7	25	<0.001

Nieminen et al., Eur Heart J 2006; 27, 2725–2736

Acute heart failure worldwide

Number of diagnosed events of AHF by country, 2004–2014

	2004	2009	2014	Growth (millions) 2004–2009	Growth (%/year) 2009–2014
USA	4,137,700	4,556,200	5,021,400	1.9	2.0
Europe	3,191,400	3,485,800	3,774,200	1.8	1.6
France	464,500	512,000	558,300	2.0	1.7
Germany	856,100	949,300	1,045,100	2.1	1.9
Italy	548,000	596,300	638,800	1.7	1.4
Spain	312,500	344,600	374,000	2.0	1.7
UK	1,010,400	1,083,600	1,157,900	1.4	1.3
Japan	799,500	810,200	811,600	0.3	0.0
Total	**8,128,700**	**8,852,000**	**9,607,200**	**1.7**	**1.7**

AHF is growing at 1.7% per year

Acute Heart Failure, December 2005. Decision Resources, Inc. 2005

PRECIPITANTS AND CAUSES OF AHF

Events usully leading to rapid deterioration
Rapid arrhythmia or severe bradicardia/conduction disturbance
ACS
Mechanical complication of ACS
Acute pulmonar embolism
Hypertensive crisis
Cardiac tamponade
Aortic dissection
Surgery and perioperative problems
Peripartum cardiomyopathy

PRECIPITANTS AND CAUSES OF AHF

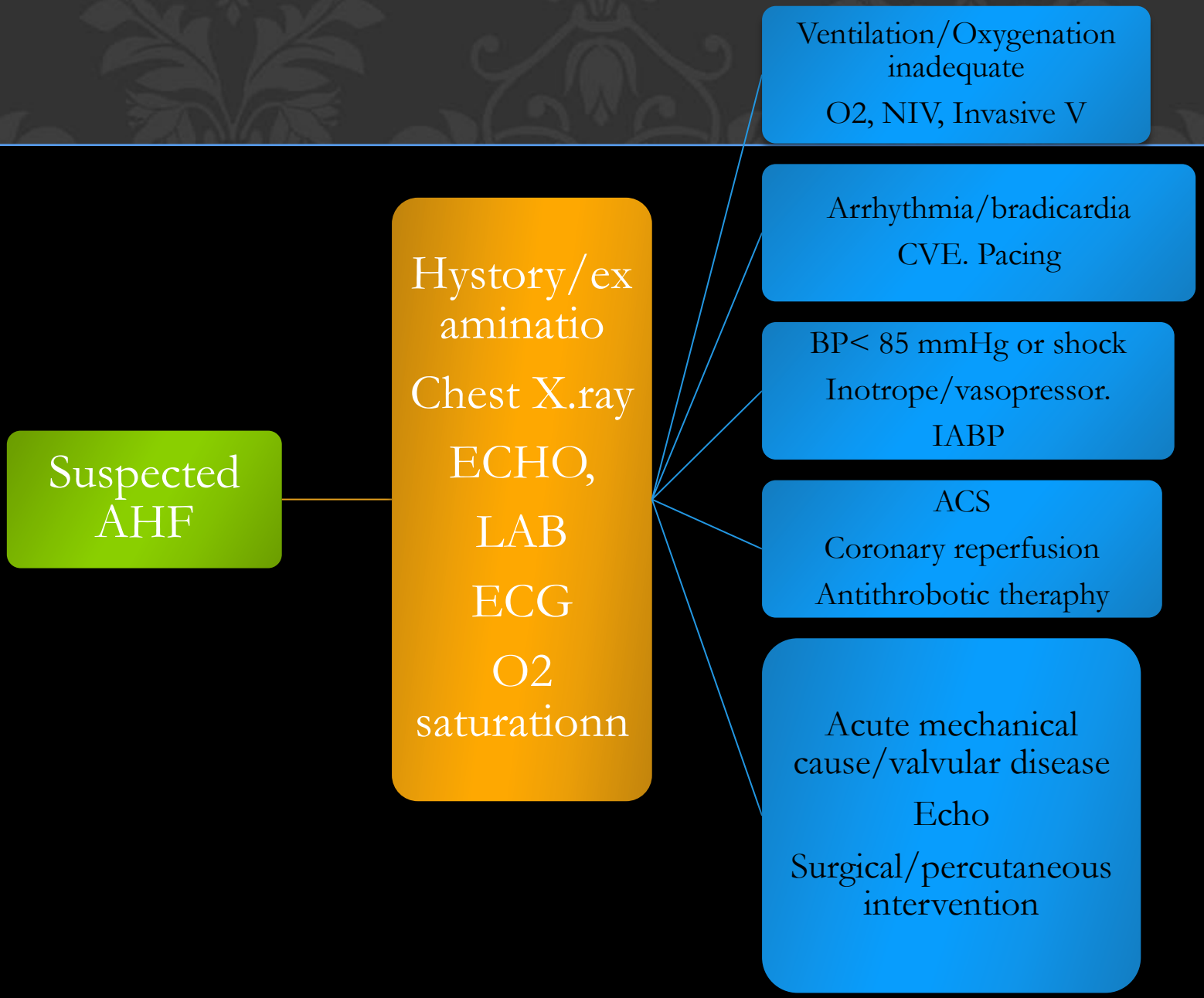
Events usully leading to less rapid deterioration
infection
COPD/Asthma
anaemia
Kidney dysfunction
Non adherence to diet and drug theraphy
Iatrogenic causes (NSAID, corticosteroid
Uncontrolled hypertension
Hypo or hyperthyroidism
Alcohol and drug abuse

INITIAL ASSESSMENT AND MONITORING
3 PARALLEL ASSESSMENTS IN INITIAL EVALUATION

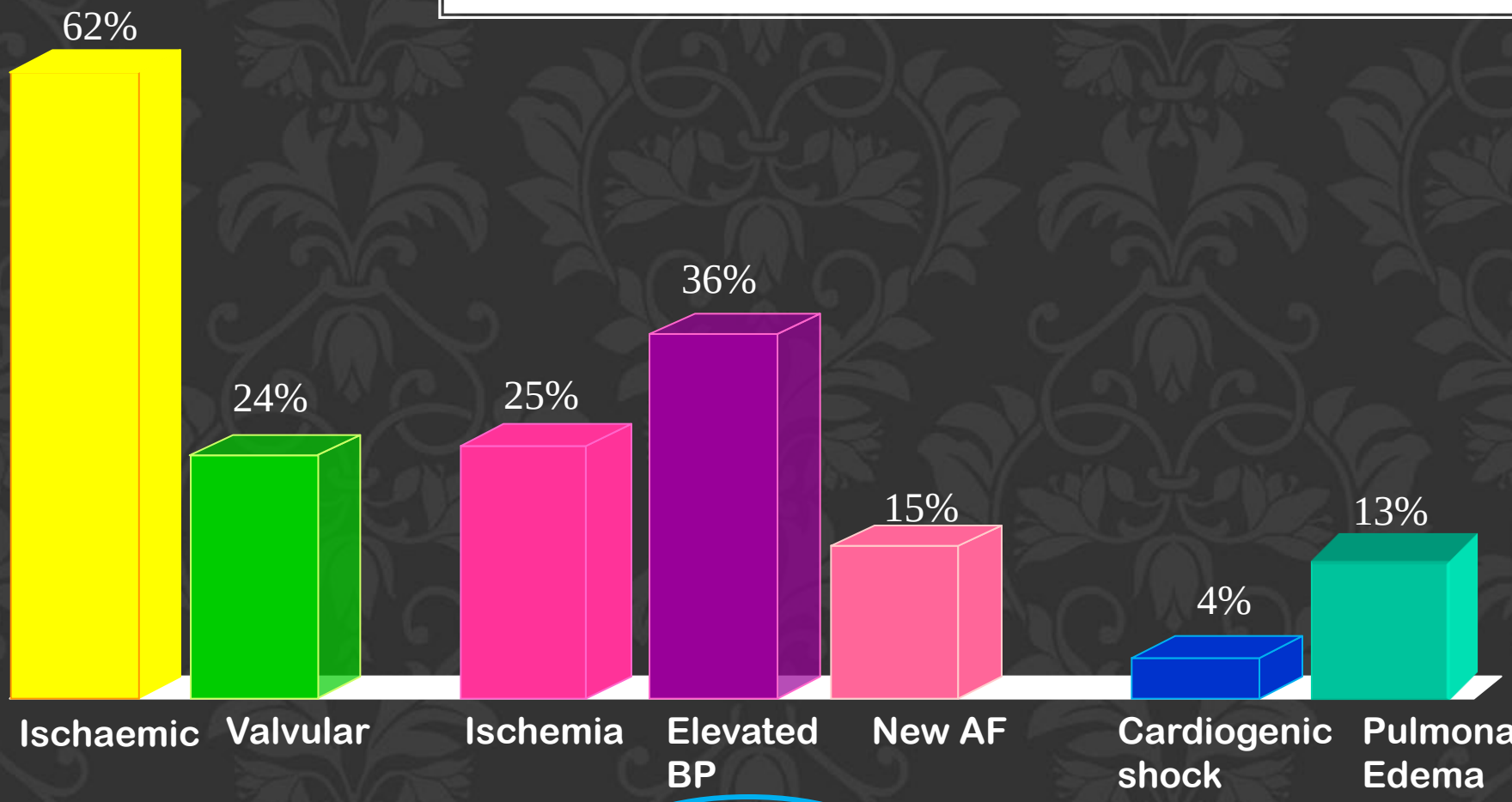
Does the patient have AHF or is there an alterative cause for SS (anaemia, kidney failure, pulmonary embolism?)

If is HF, is there a precipitant and does it require immediate R/ (ACS, arrhythmia)?

Is condition immediately life-threatening because of hypotension or hypoxaemia leading to underperfusion of vital organs ?

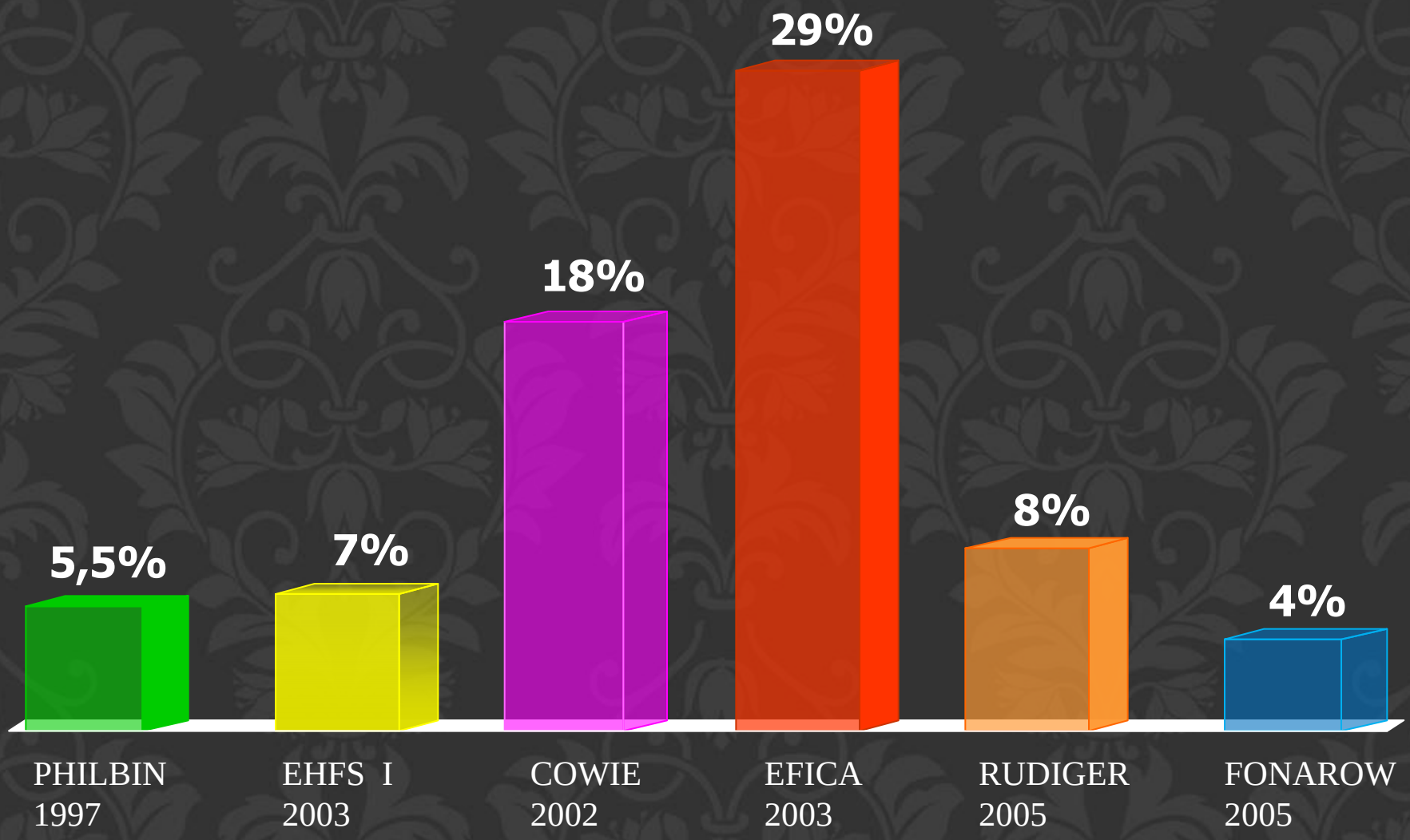

Suspected AHF
Hystory/examinatio
Chest X.ray
ECHO,
LAB
ECG
O2 saturationn
Ventilation/Oxygenation inadequate
O2, NIV, Invasive V
Arrhythmia/bradicardia
CVE. Pacing
BP< 85 mmHg or shock
Inotrope/vasopressor.
IABP
ACS
Coronary reperfusion
Antithrobotic theraphy
Acute mechanical cause/valvular disease
Echo
Surgical/percutaneous intervention

ACUTE HEART FAILURE

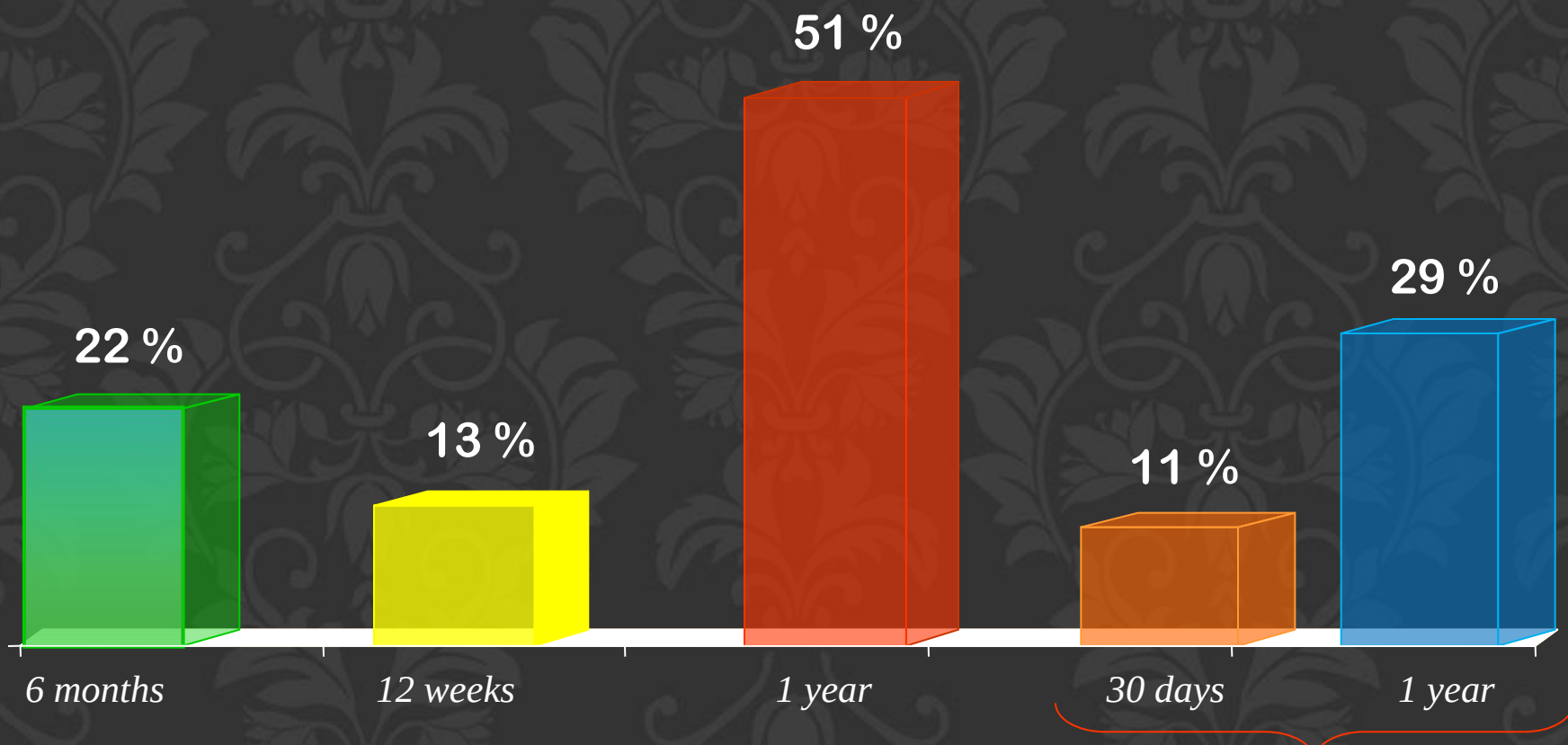


Rudiger, Eur. J. Heart Fail., 2005

IN HOSPITAL MORTALITY



SHORT-MEDIUM TERM MORTALITY



PHILBIN
1997

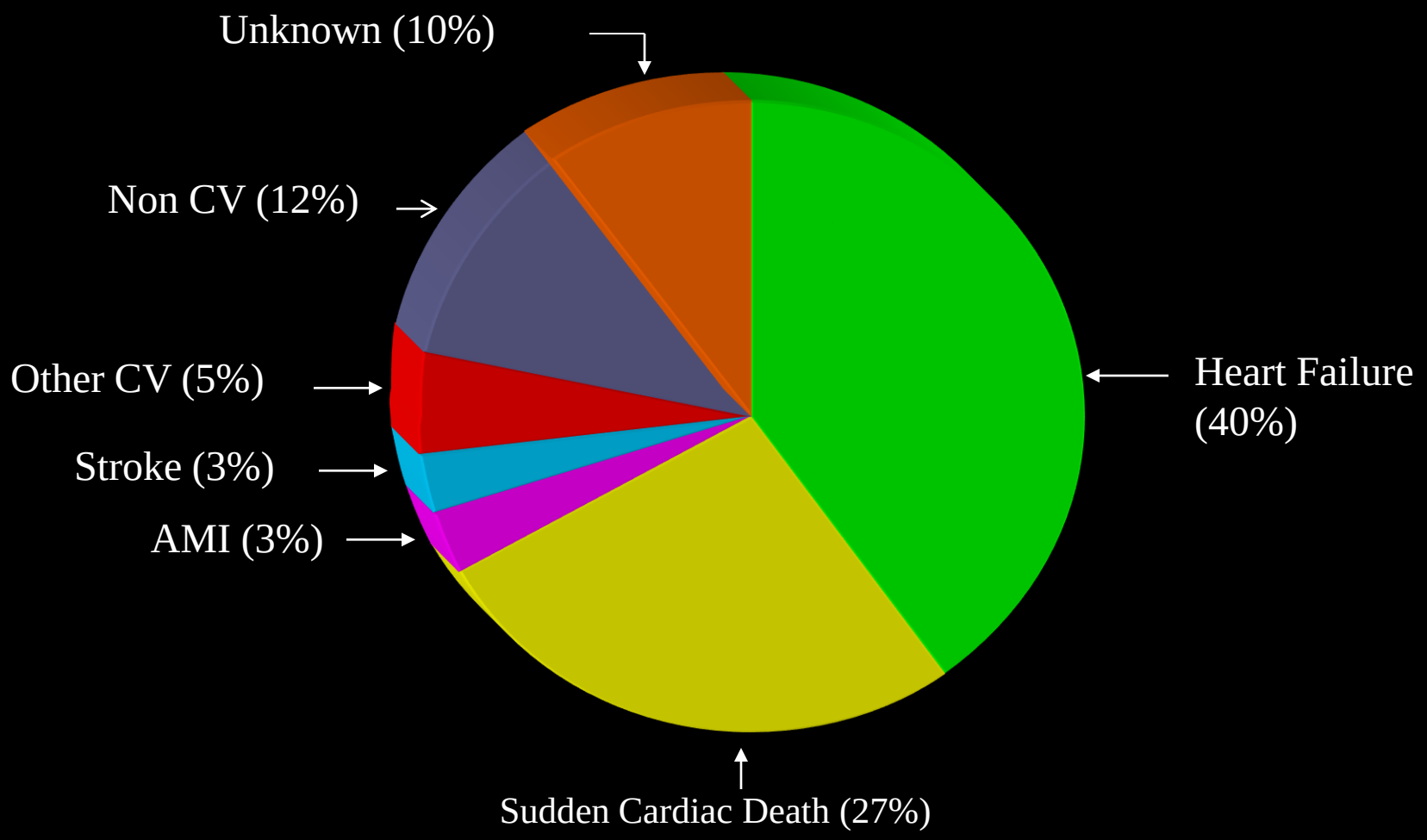
EHFS I
2003

EFICA
2003

RUDIGER
2005

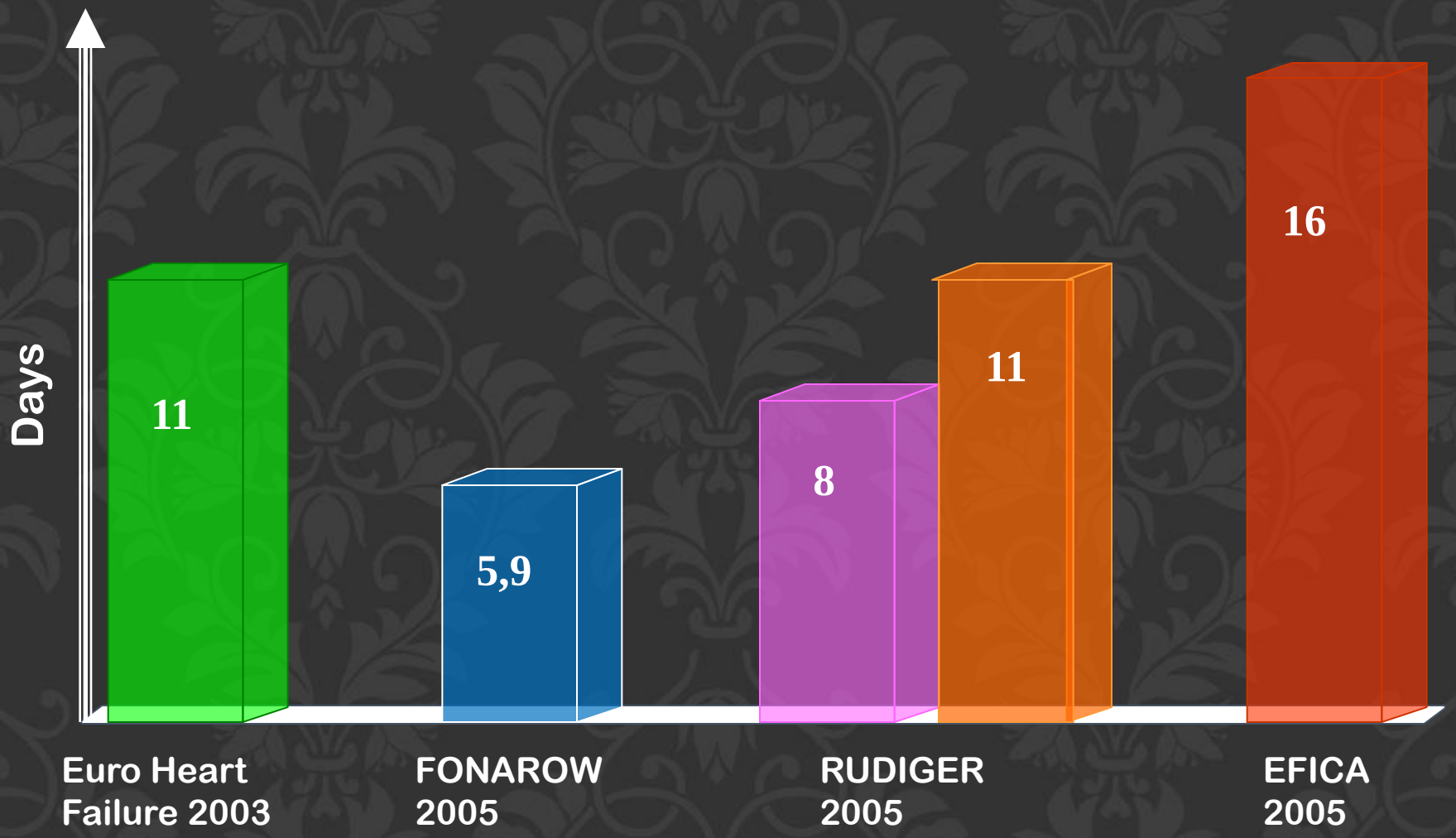
Adjudicated Cause of Death after Discharge in 4,133 Pts Hospitalized with Worsening HF and low EF:

Over-all mortality rate of 26% at 10 months follow-up

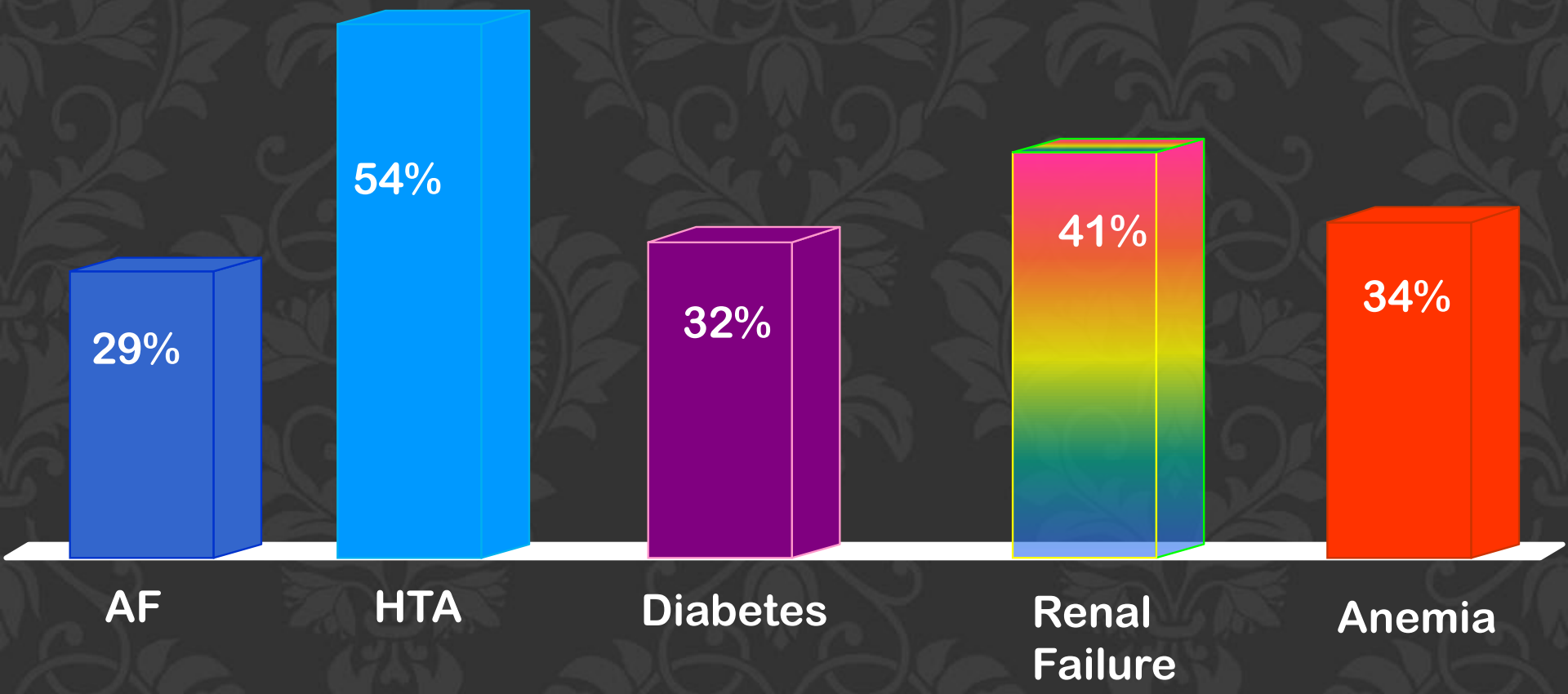


O'Connor et al. ESC 2008

LENGTH OF STAY

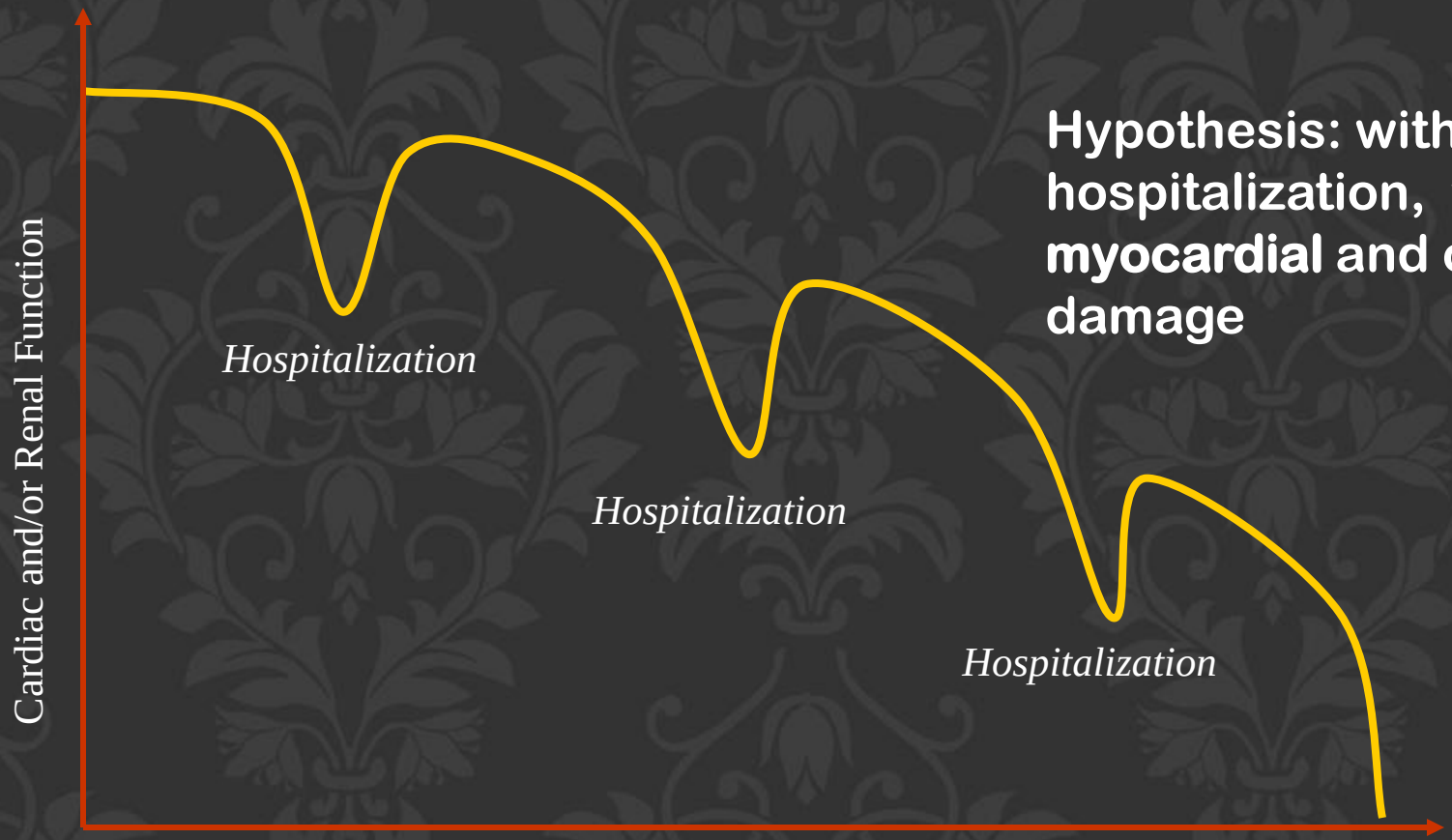


ACUTE HEART FAILURE COMORBIDITIES



Rudiger, Eur. J. Heart Fail., 2005

AHFS and Progression of HF : a major clinical challenge



Hypothesis: with each hospitalization, there is myocardial and or renal damage

Gheorghiade M et al. Am J Cardiol. 2005; 96 (6A)

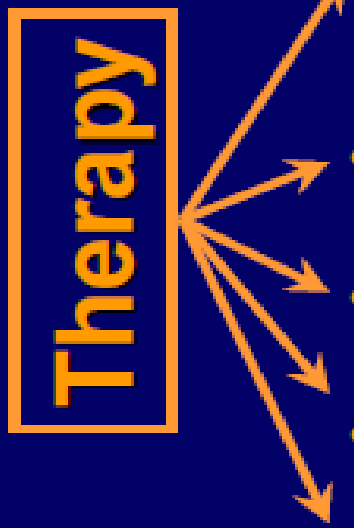
AIM FOR TREATMENT IN AHF

Improve haemodynamics, diuresis and neuroendrocine system

Clinical improvement, quality of life and/or mortality

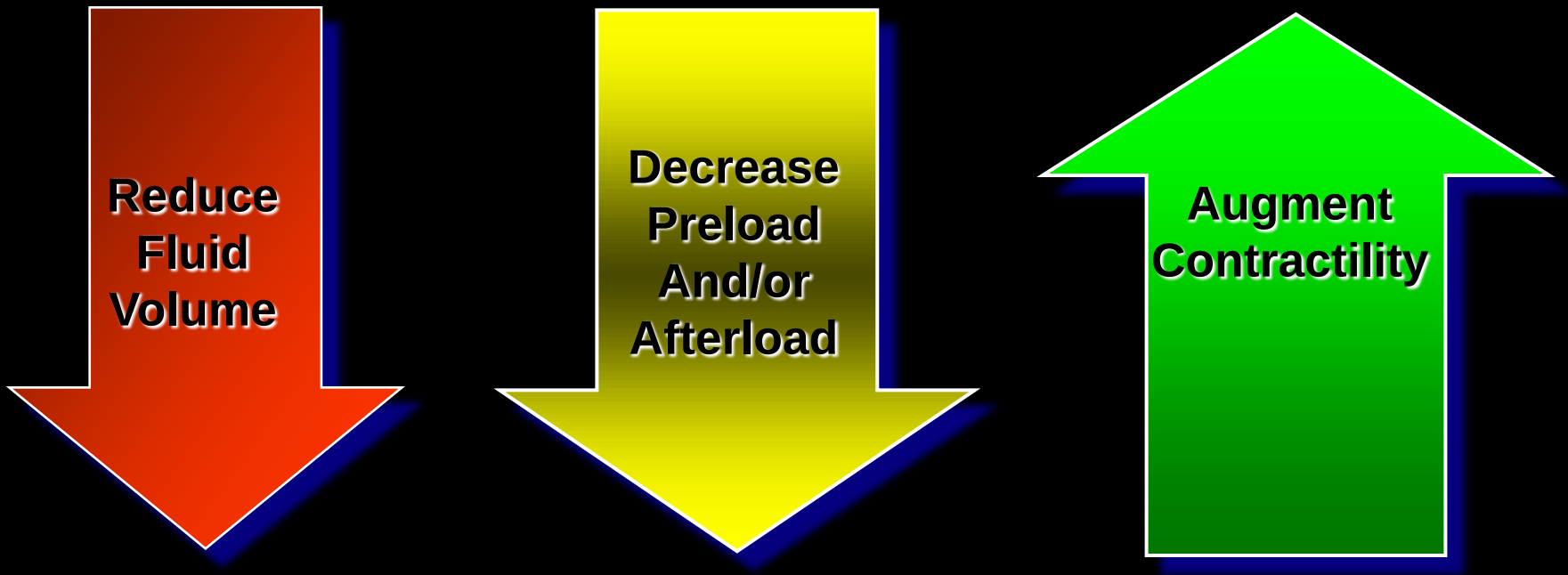
Safety

Pathophysiologic mechanisms in acute HF

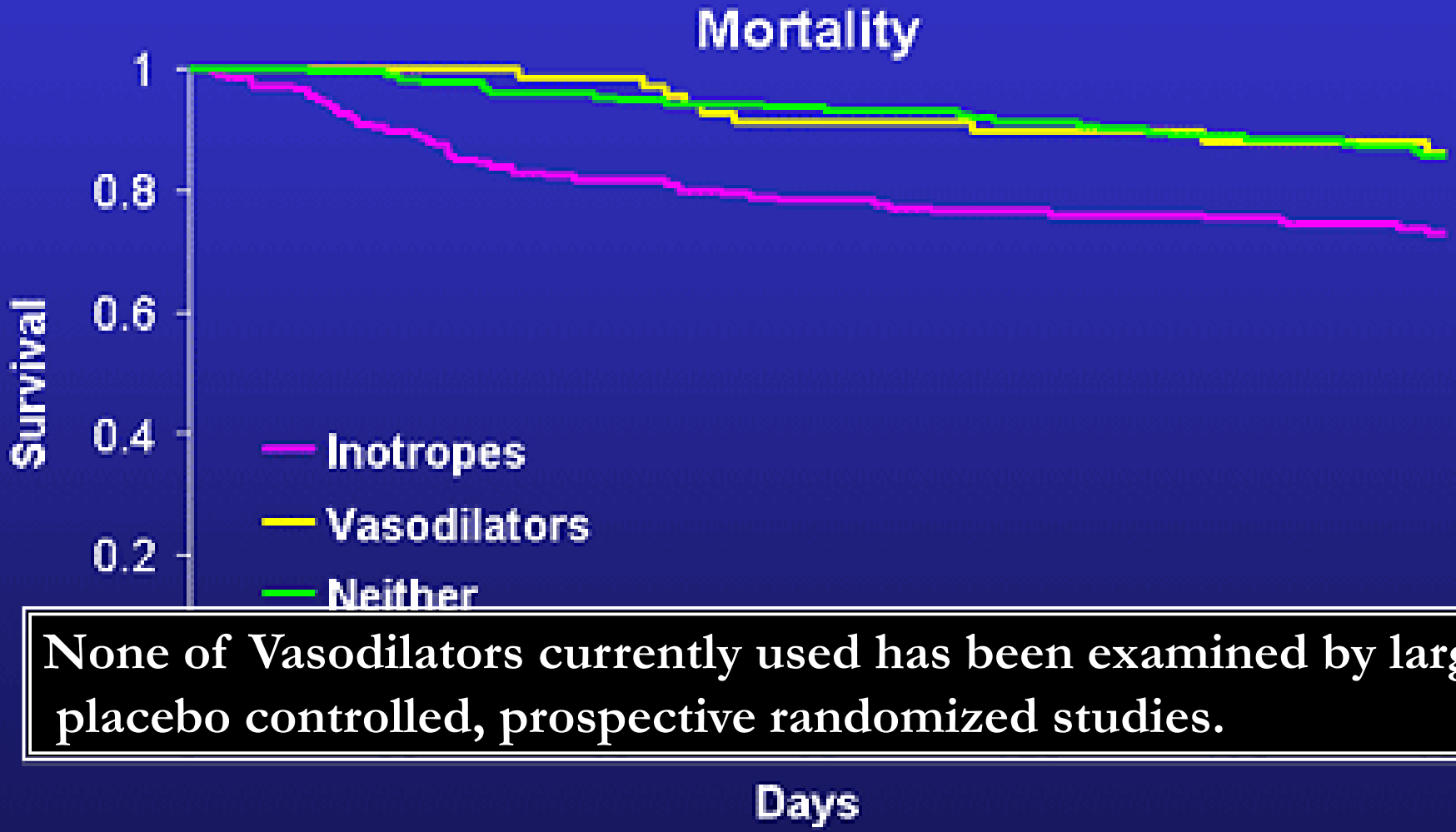


- Myocardial injury – cell death
  - Ischaemia / Apoptosis
- Arrhythmias
- Renal dysfunction
- Hypotension / Hypoperfusion
- …..

CURRENT TREATMENTS FOR ACUTE HF



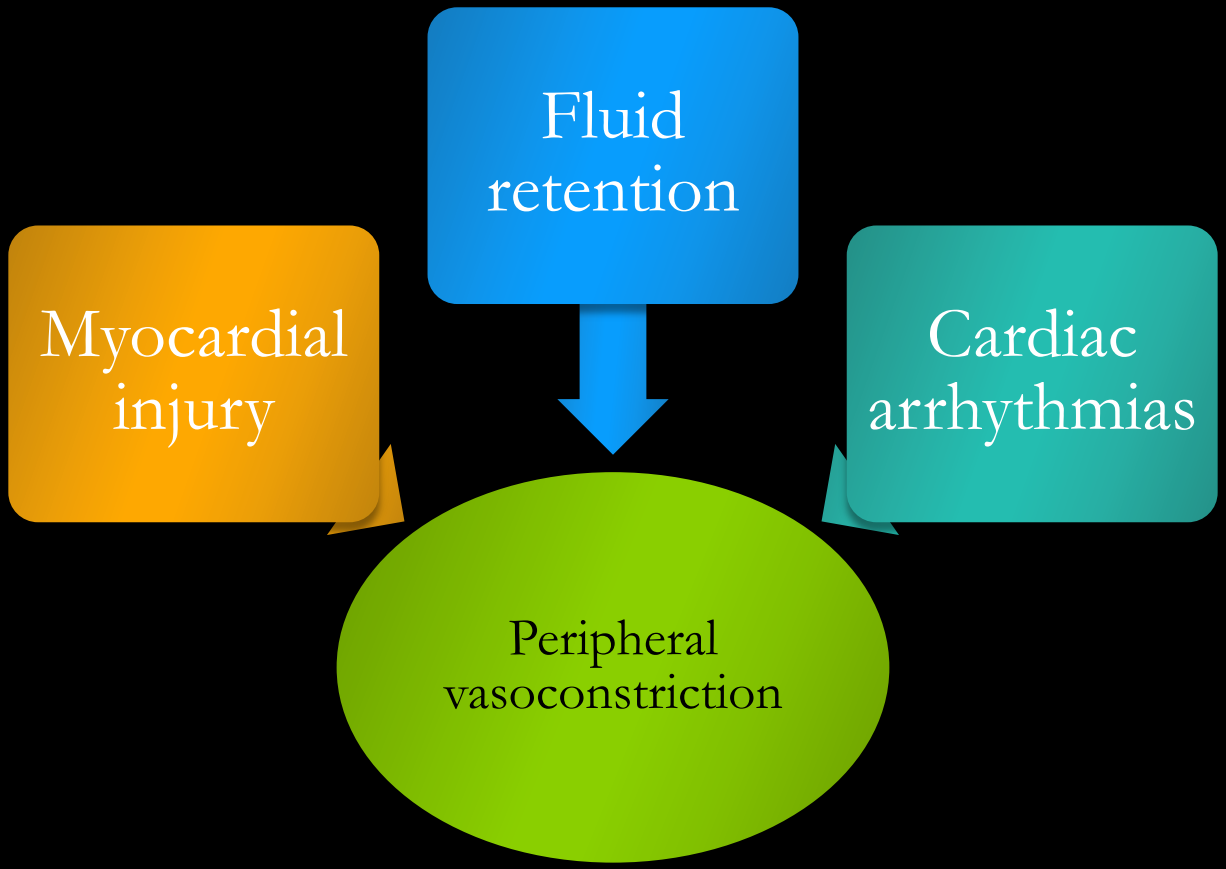
ESCAPE: Kaplan-Meier Survival By IV Medication Use



None of Vasodilators currently used has been examined by large, placebo controlled, prospective randomized studies.

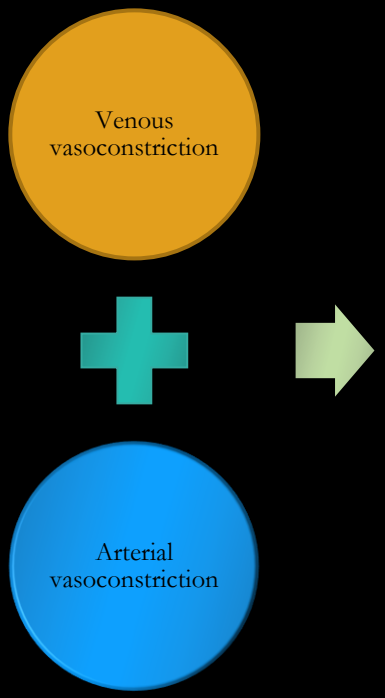
Elkayam U et al. *Circulation*. 2004;110(17 suppl):III-515

CENTRAL ROLE OF VASOCONSTRICTION



Interaction between a progressive decrease in cardiac performance and an acute increase in SVR, so called “afterload mismatch”

CENTRAL ROLE OF VASOCONSTRICTION IN PATHOGENESIS OF AHF



INCREASED VENOUS PRESSURE

- Peripheral edema
- Redistribution of peripheral venous blood into pulmonary vasculature
- Pulmonary edema
- Increased preload
- REGIONAL ARTERIAL VASOCONSTRITION
- Increase afterload
- Increase myocardial workload
- Increase myocardial wall tension
- Regional arterial vasoconstriction
- Renal failure
- Cerebral hypo perfusion
- ACS
- Stimulation of chronic vascular remodeling

about 90% pts have BP normal / high at admission

HOSPITAL DE SANTAMARIA

NEUROHORMONAL PLAYERS IN HF

- Vasoconstrictor systems
  - Sympathetic
  - Renin-angiotensin
  - Aldosterone
  - Endothelin
  - vasopressin
- Vasodilators systems
  - Bradykinin
  - Nitric oxide
  - Prostacyclin
  - Natriuretic peptides

Powerful neurohormones vasoconstrictor forces dominates

HOSPITAL DE SANTAMARIA

Ideal Agent for AHF treatment

The Saint Graal ?

Vasodilation (venous and arterial)

Rapidly decreases ventricular filling pressures and congestion

Does not increase heart rate or directly increase contractility (decreases myocardial oxygen demand)

Is not proarrhythmic

Has no tachyphylaxis

Provides neurohormonal suppression

Promotes diuresis/natriuresis

Is conveniently dosed (can be used with or without pulmonary artery catheterization)

Minimal titration needed

POTENTIAL RISKS AND BENEFITS OF VASODILATORS IN AHF

Makes patients feel better, early and sustained relief of dyspnea

Possibility of hypotension, worsening renal function, myocardial damage. May cause "coronary steal" and be harmful in pts with ongoing ischemia

May have a U-shaped dose-effects relationships, high doses may reduce their effectiveness , because of counter regulatory mechanisms, induce rebound neurohormonal activation pottentially limiting short and long term efficacy

In pts with AHF with reduced cardiac reserve, vasodilators nay induce a steep reduction in BP, inappropriate vasodilatation, ischemia, renal failure and sometimes shock,.

ORGANIC NITRATES

Used for more than 100 years

Biotransformation mainly in the smooth muscle intracellular space, leading to formation of ON or a related S-nitrosothiol, which stimulates guanylate cyclase

Reduces intracellular calcium levels which leads to venous and arterial vasodilatation

Promotes endothelial production of prostacyclin

TRADITIONAL VASODILATORS

AHF without Hypotension

class I, B

Nitroglycerine and ISD

Exerting a predominant venodilator effect at low doses and mild arteriolar effect at higher doses

↙ **R & LVF pressures, PVR, SVR, wall stress, pulmonary congestion, without compromising stroke volume or increasing myocardial oxygen consumption**

Decrease BP, but little or no change in HR

Reduces Mitral Regurgitation

ORGANIC NITRATES: NEUROHORMONAL EFFECTS

Reduction OF plasma natriuretic peptide BUT small increase aldosterone, cortisol, epinephrine and plasma renin

Dilatation of main renal artery

Early development of tolerance and marked attenuation of initial hemodynamic effects in half pts with AHF

TRADITIONAL VASODILATORS

AHF without Hypotension

Careful monitoring of BP
High doses may reduce effectiveness because of counter regulatory mechanisms

Use with caution in pts who really deserve them, using right doses, monitoring and carefull titulation

NITROPRUSSIDE

Salt of complex molecule made up of ferric cyanide

Production of nitrosothiol and GMPc in vascular smooth muscle

Reduces elevated filling pressures, increase venous capacitance

Reduces afterload of right and LV

Significant reduction in BP, RAP, PCWP, SVR and PVR. Increase CO

Effect on coronary blood flow in pts with CAD may be determinated by more vasodilatory effect on nonobstructed coronary beds

VASODILATORES TRADICIONAIS:

Nitroprussiato, class IC

- Potente vasodilatador arterial e venoso
- Pequenos estudos

Melhoria hemodinâmica

Difícil titulação, (± linha arterial)

Resposta neuro-hormonai; Aumento NE, renina,

NITROPRUSSIDE

Treatment of ADHF and Acute Valvular Regurgitation.

Can cause rebound effects-gradual discontinuation

Can effectively augment hemodynamic effects of inotropic agents.

The incidence of side effects and toxicity is dose and duration related

Side effects of thiocyanate toxicity (> 6 mg): metabolic acidosis- can be removed by hemodialisis and treated with hydroxycobalamin

Conversion of cyanide to prussic acid incresase methemoglobin levels

These effects are rare if we use NTP < 3 ng/Kg/min e < 72 hours

Vasodilators in AHF

Drug	PWP / RAP	SVR	CO / SV	Congest.	Hypoperf.
Nitrates (GTN, I-5MN, IDN)	↓↓↓↓	↓↓	↑	↓↓	↓
Nesiritide*	↓↓↓↓↓	↓↓	↑	↓↓↓	↓
Nitroprusside	↓↓	↓↓↓	↑↑↑	↓	↓
*Endothelin antagonists***	↓↓	↓↓↓	↑↑↑	↓	↓

* Not approved in most European countries
** Not approved for clinical use

Drug	Indication	Regimen	Adverse effects	Limitations
nitroglycerine	**Acute PE; pulmonary congestion in normo or hypertensive AHF**	10-20 ug/min, increase up to 200 ug/min	Hypotension Headache	Tolerance is common after 24-48 h, requiring adjustment of dosing
ISD	**Pulomonary Edema Pulmonary congestion normo/HBP**	1 mg/h, increase up to 10 mg/h	Hypotension Headache	Tolerance as for nitroglycerine
Nitroprusside	**Acute hypertensive congestion due to acute mitral Regurgitation**	0,3ng/Kg/min Increase up to 5 mg/Kg/min	Hypotension Isocyanate toxicity	Light sensitive Arterial line is necessary for BP monitoring
neseritide	Pulmonary edema Pulmonary	Bolus and perfusion 0,015-0,030	Hypotension Worsening renal function	Not available in ESC countries

ACTIONS OF HUMAN BNP

ENDOGENOUS BNP IS AN ADAPTIVE RESPONSE TO PRESSURE AND VOLUME OVERLOAD

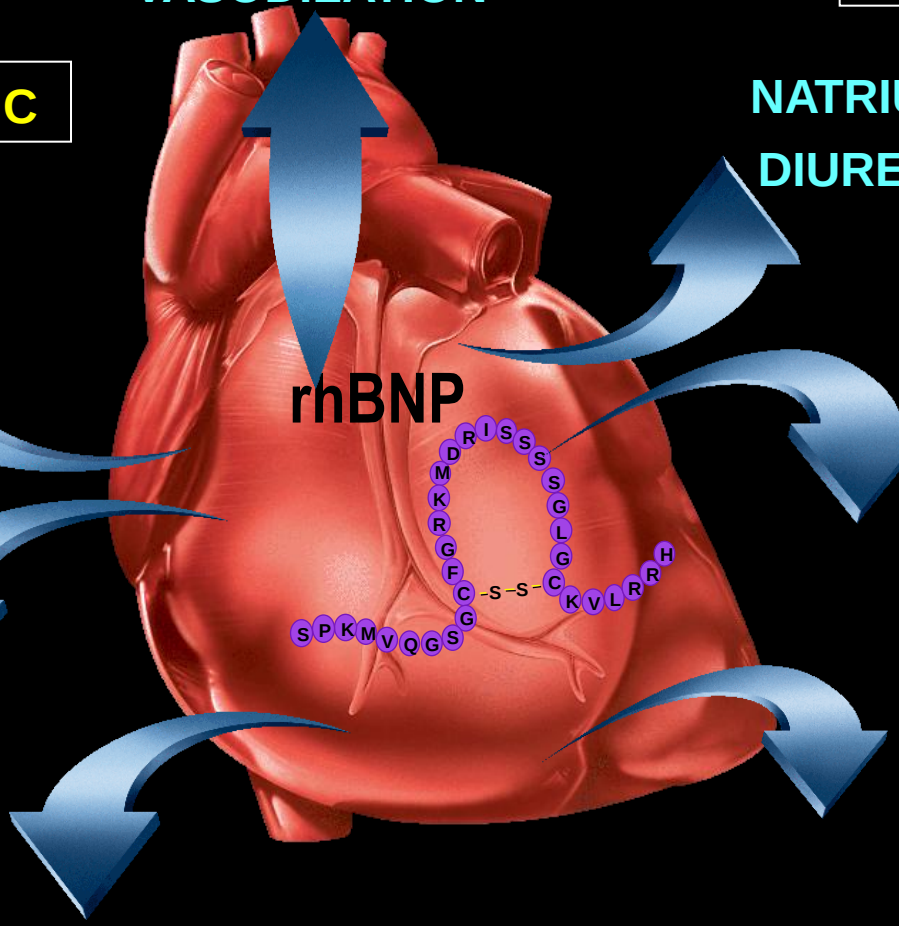
Venous, arterial, coronary
VASODILATION

RENAL

HEMODYNAMIC

NATRIURESIS
DIURESIS

CARDIAC INDEX



Fluid volume
Preload
Diuretic usage

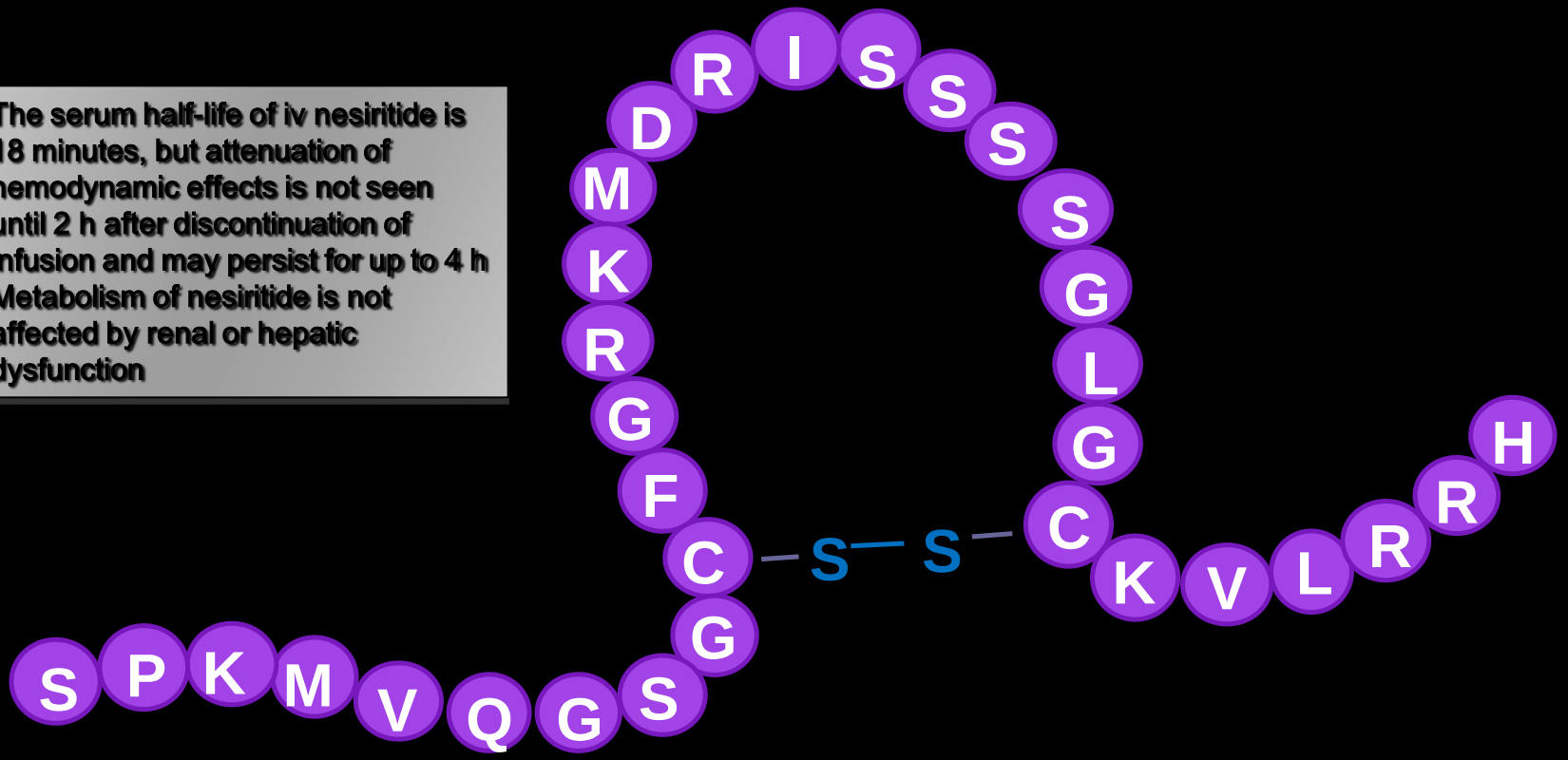
Preload
Afterload
PCWP
Dyspnea

CARDIAC

SYMPATHETIC AND NEUROHORMONAL MODULATION

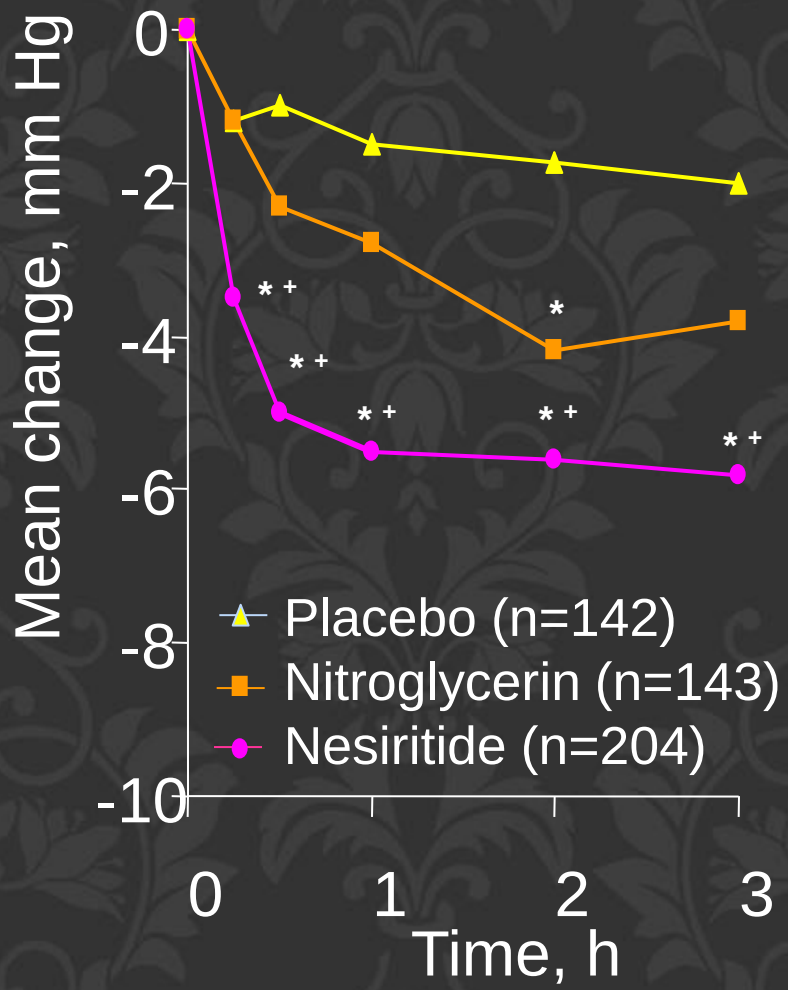
Nesiritide (h-BNP) is identical to the endogenous naturally occurring hormone, with identical pharmacological profile

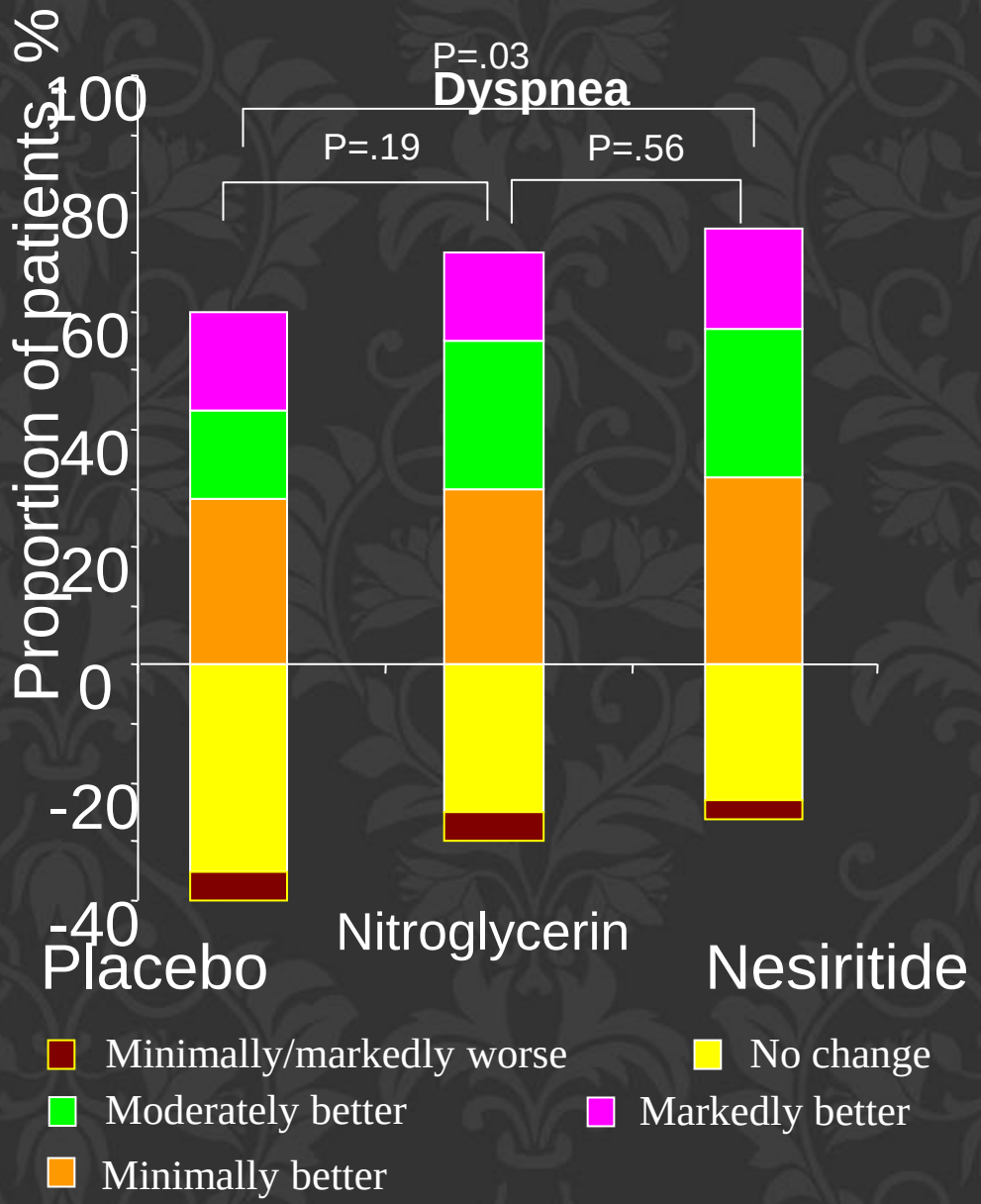
The serum half-life of iv nesiritide is 18 minutes, but attenuation of hemodynamic effects is not seen until 2 h after discontinuation of infusion and may persist for up to 4 h Metabolism of nesiritide is not affected by renal or hepatic dysfunction



NOTE: hBNP affects assay for BNP, but can still use proBNP or one of the proANP assays

Intravenous Nesiritide versus Nitroglycerin for the Treatment of Decompensated Heart Failure – VMAC trial

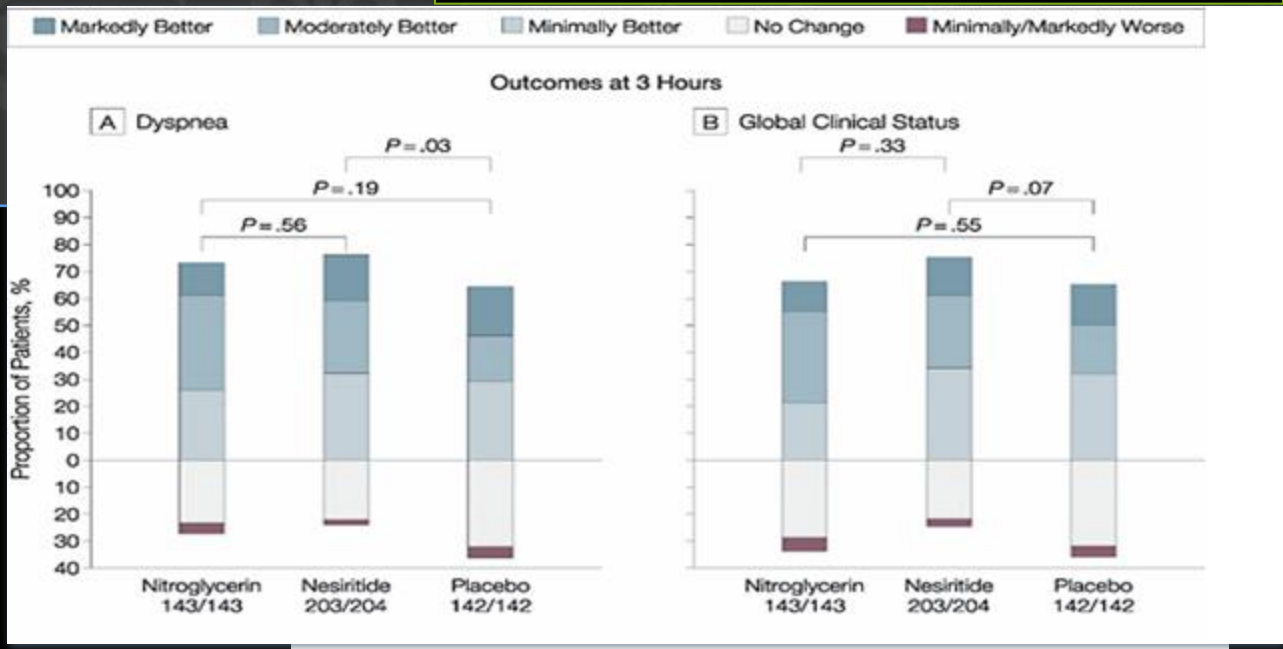




VMAC - Nesiritide

Dyspnea Improvement in VMAC

Critical look – minimal dyspnea improvement With worsening renal function and increased mortality



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure

Jonathan D. Sackner-Bernstein, Hal A. Skopicki and Keith D. Aaronson

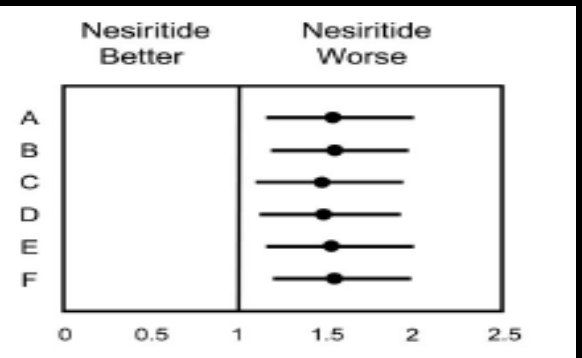
Circulation 2005;111;1487-1491; originally published online Mar 21, 2005;
DOI: 10.1161/01.CIR.0000159340.93220.E4
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75214

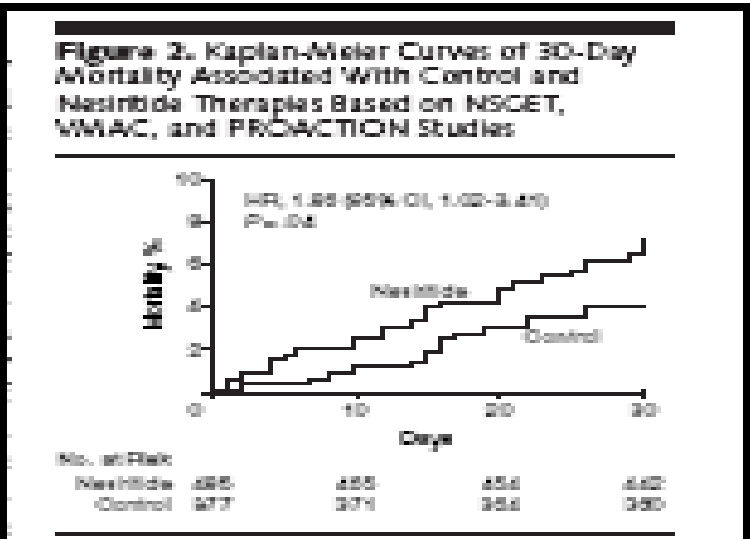
JAMA
Online article and related content current as of October 5, 2008.

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure: A Pooled Analysis of Randomized Controlled Trials

Jonathan D. Sackner-Bernstein; Marcin Kowalski; Marshal Fox; et al.

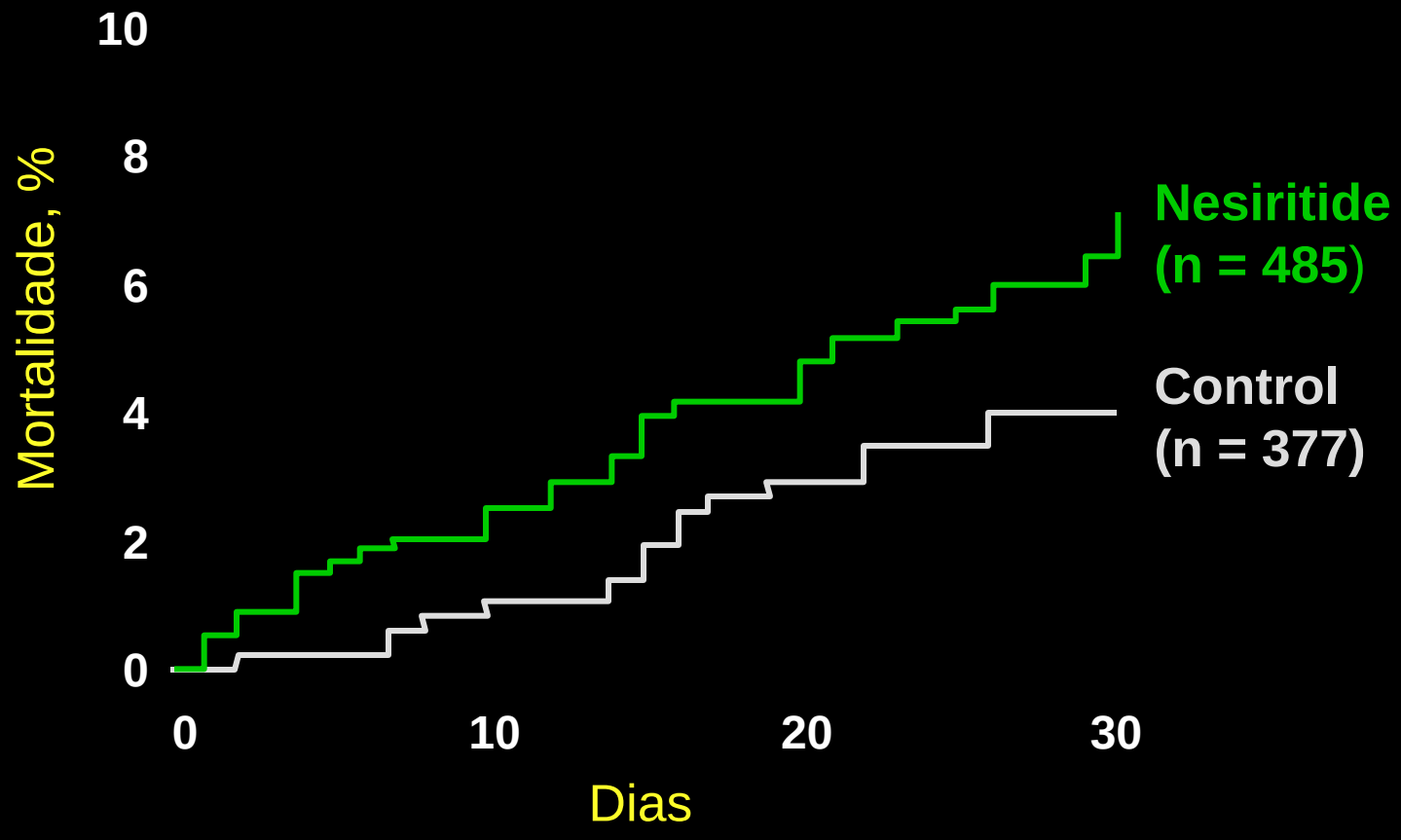
JAMA. 2005;293(15):1900-1905 (doi:10.1001/jama.293.15.1900)
http://jama.ama-assn.org/cgi/content/full/293/15/1900





EFEITO DO NESIRITIDE NA MORTALIDADE A CURTO PRAZO (30 DIAS)

Sugere que nesiritide aumenta a mortalidade a curto prazo



Acute Study of Effectiveness of Nesiritide in Decompensated Heart Failure

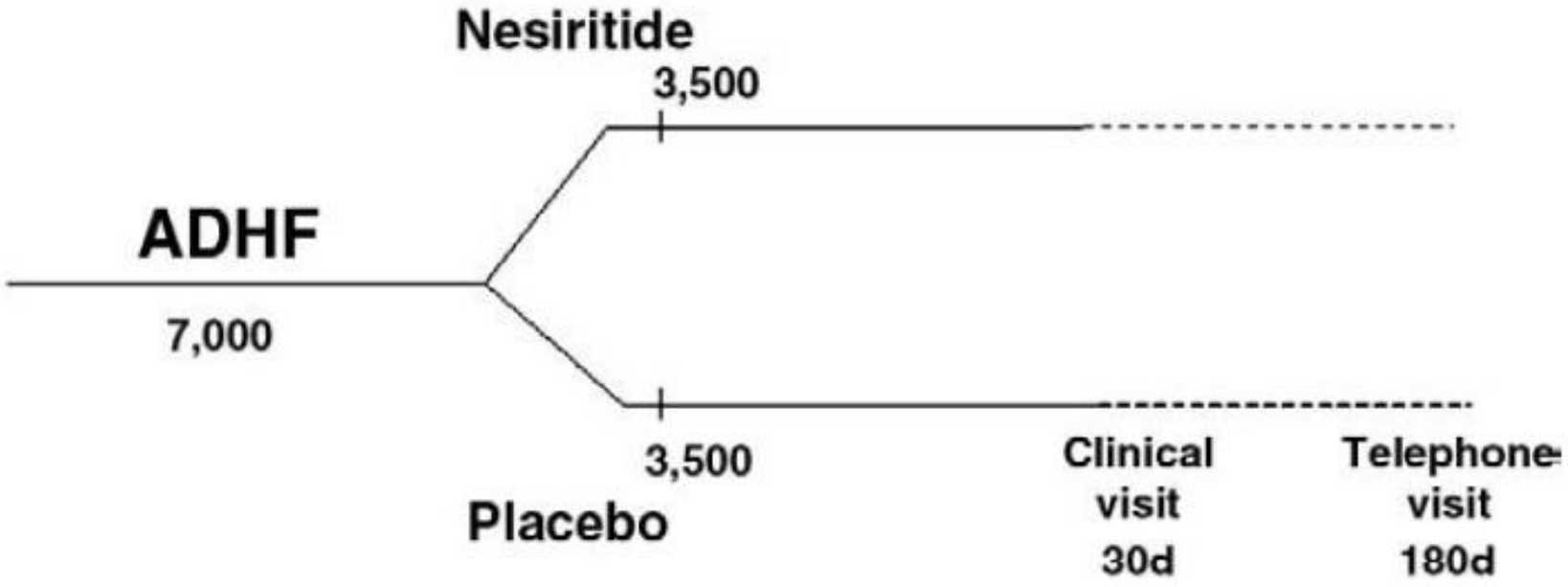
Adrian F. Hernandez, MD

On behalf of the ASCEND-HF Committees, Investigators and Study Coordinators

ASCEND-HF design

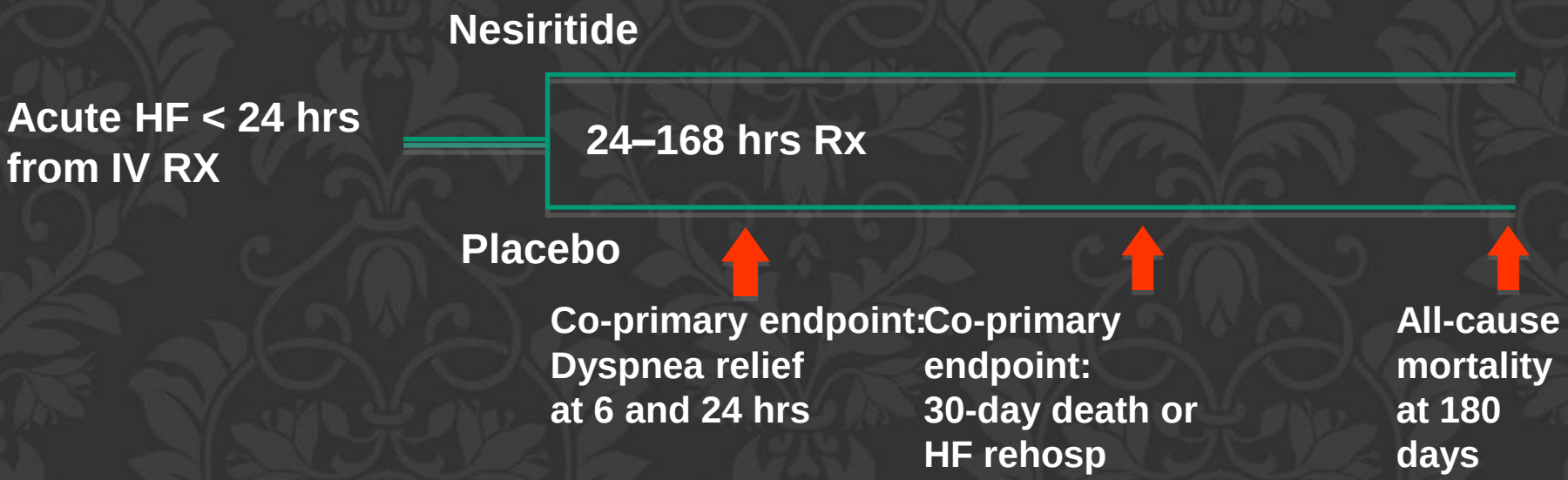
HF rehospitalization and Death at 30 days Co-primary endpoint	Dyespnea at 6 or 24 hours after study drug initiaition Co-primary endpoint

completed in 2010
 # 7000 pts enrolled



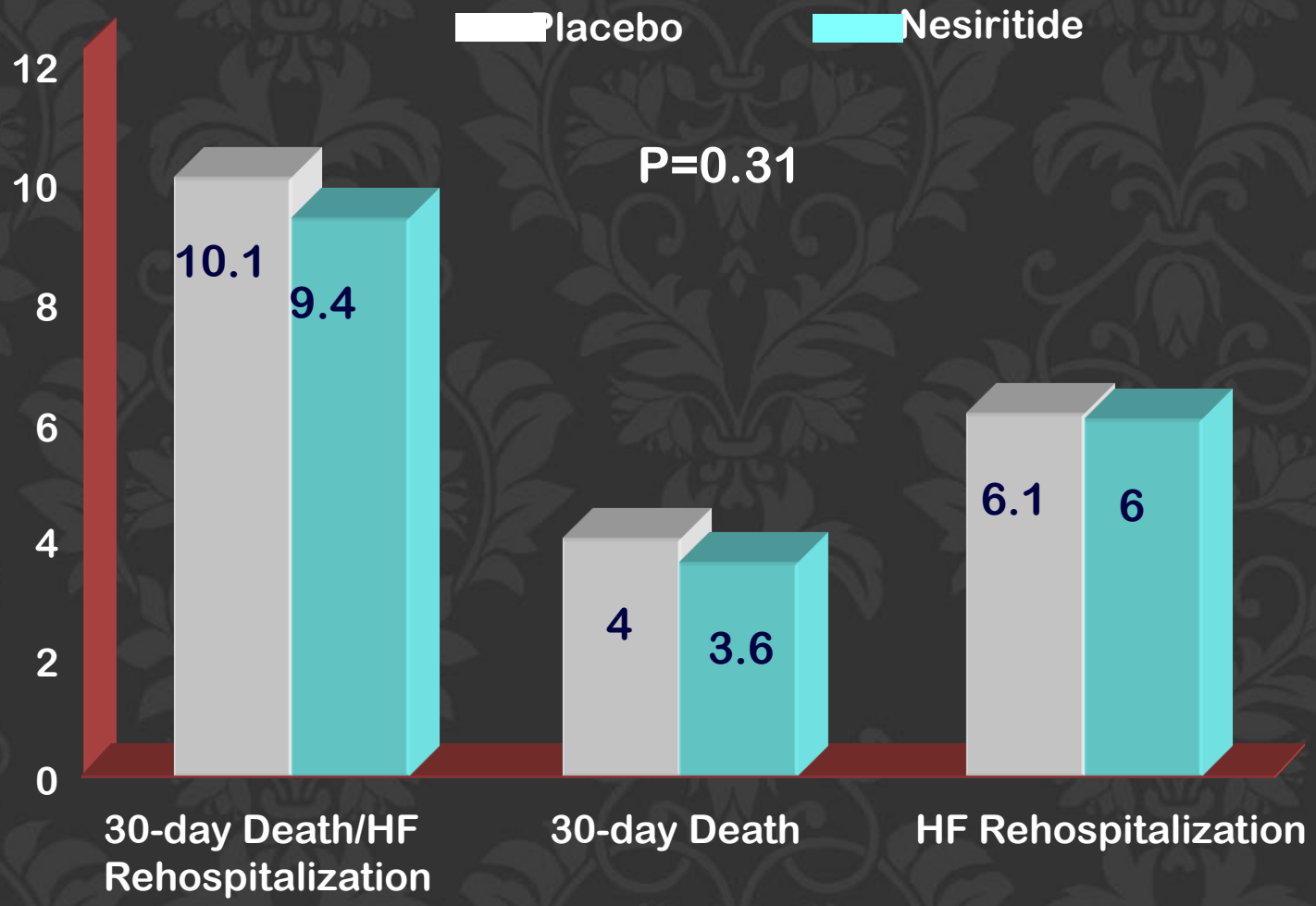
Overall trial design for ASCEND-HF.

Study design and drug procedures



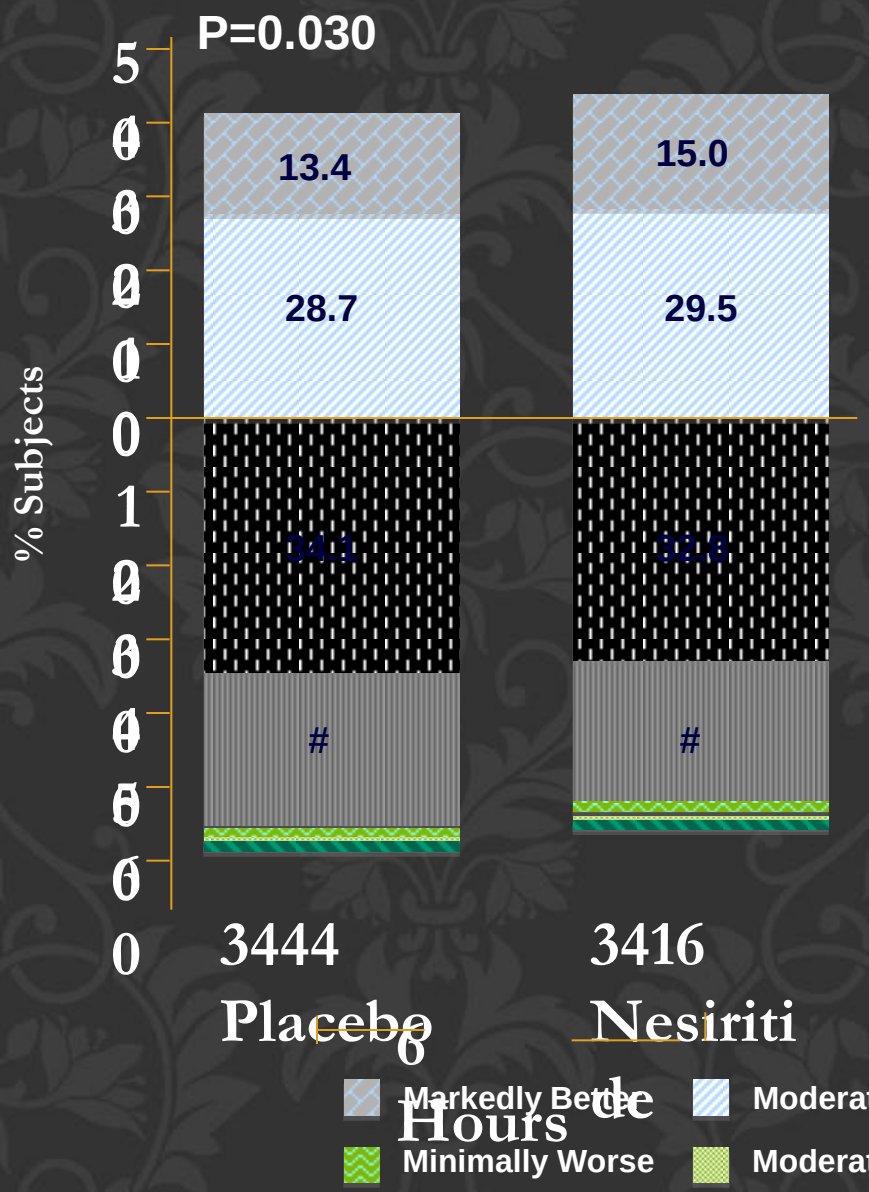
- Double – blind placebo controlled
- IV bolus (loading dose) of 2 µg/kg nesiritide or placebo
  - Investigator's discretion for bolus
  - Followed by continuous IV infusion of nesiritide 0.01 µg/kg/min or placebo *for up to 7 days*
- Usual care per investigators including diuretics and/or other therapies as needed
- Duration of treatment based on clinical improvement per investigator

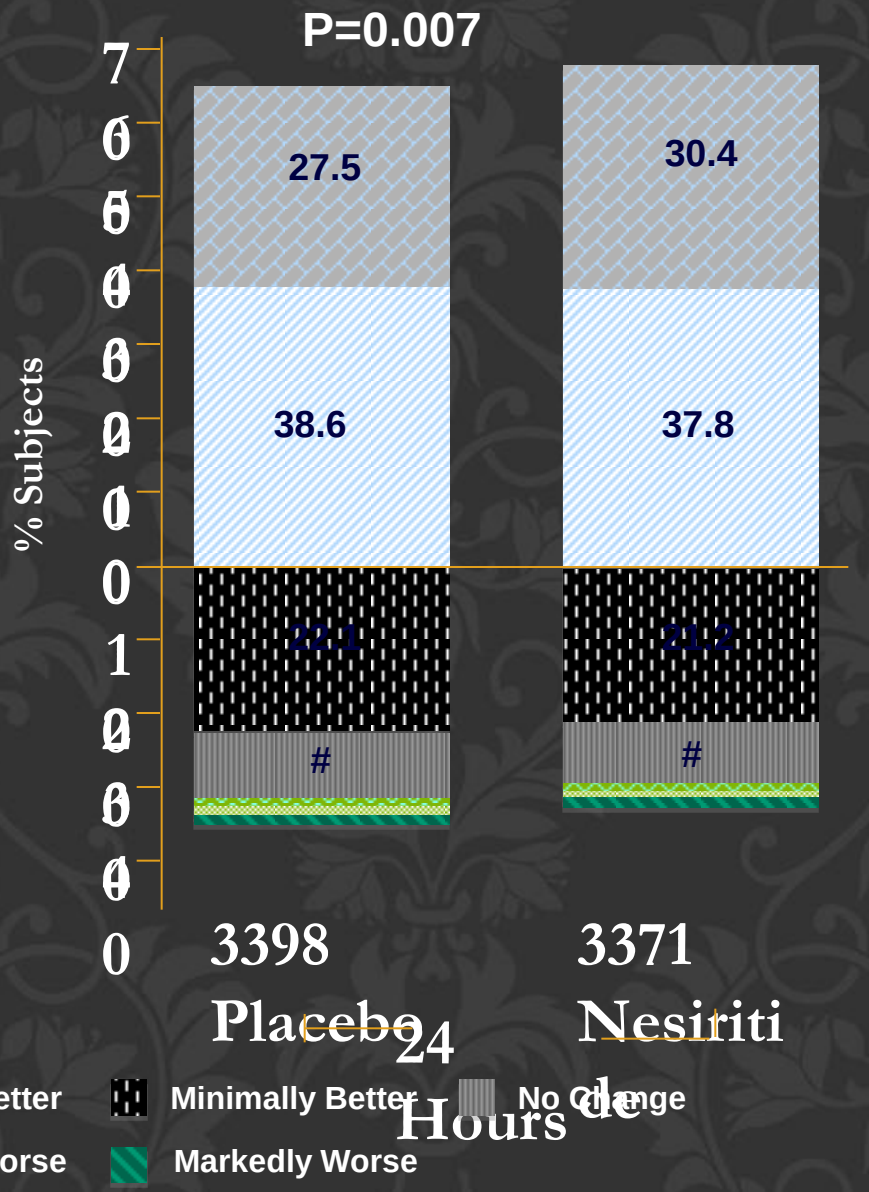
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization



Risk Diff 95 % CI	-0.7 (-2.1; 0.7)	-0.4 (-1.3; 0.5)	-0.1 (-1.2; 1.0)

Co-Primary Endpoint: 6 and 24 hour dyspnea



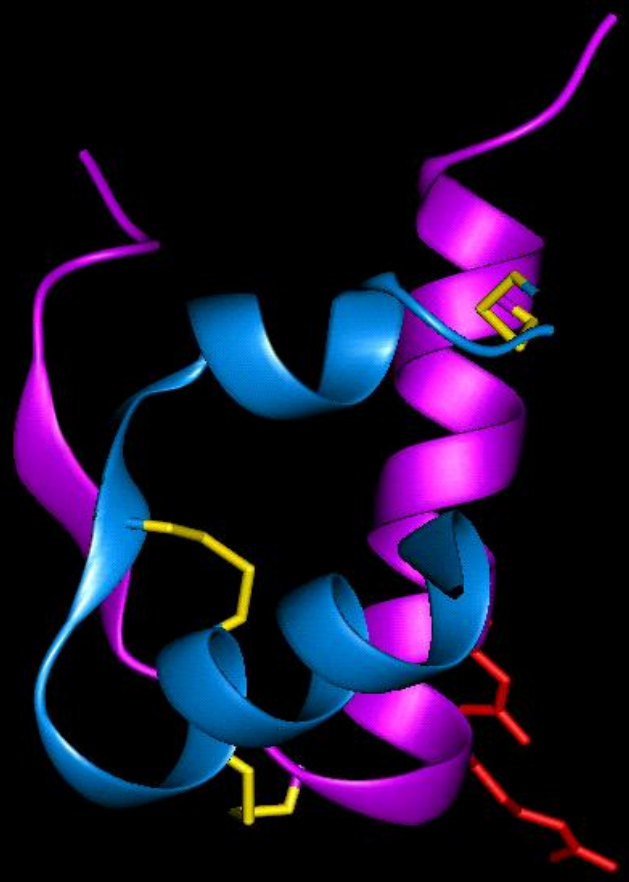


RELAXIN, A NOVEL TREATMENT FOR ACUTE HEART FAILURE-

THE PRE-RELAX-AHF STUDY

John R. Teerlink, Marco Metra, G. Michael Felker,
Adriaan A. Voors, Piotr Ponikowski, Beth D. Weatherley,
Elaine Unemori, Sam L.Teichman, and Gad Cotter
on behalf of the
Pre-RELAX-AHF Investigators & Patients

RELAXIN MECHANISMS OF ACTION



Naturally occurring peptide

Up-regulated in pregnancy and HF

Vasodilation…

Upregulation of ETB

Induction of NOS II/III

NO, cGMP effectors

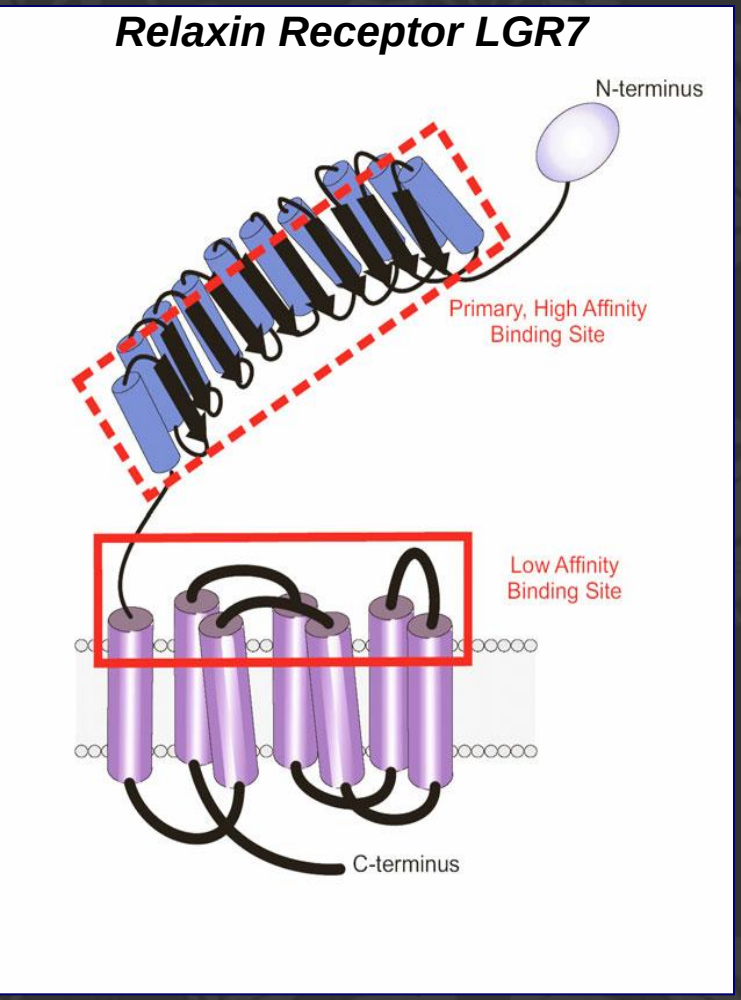
…but actually an anti-vasocontrictor - Preferential dilates constricted vessels

Anti-ischemic effects in animal models

Anti-inflammatory

Down-modulation of inflammatory cytokines linked to outcome in HF (TNF-a, TGF-b)

RELAXIN MECHANISMS OF ACTION



- **Vasodilation**
  - NO, cGMP effectors
  - Induction of NOS II/III
  - Upregulation of endothelial endothelin type B receptor, which mediates vasodilation
- **Preferential dilation of constricted vessels**
  - Relaxin-upregulated ET_B receptors act as vasodilating ET-1 sink
- **Anti-inflammatory**
  - Down-modulation of inflammatory cytokines linked to outcome in HF (TNF-α, TGF-β)
- **Other: Anti-ischemic, Anti-apoptotic, Anti-fibrotic**

Teichman, SL, et al. Heart Fail Rev 2009; Dschietzig, T, et al. Pharmacol Therap 2006

GLOBAL PHASE 2 IN ACUTE HEART FAILURE

Study Design

- Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, International Study
- Randomized to placebo, 10, 30, 100, 250 µg/kg of relaxin (3,2,2,2,2) – 48 hr iv infusion, on top of standard of care
- 234 patients, 54 sites, 8 countries

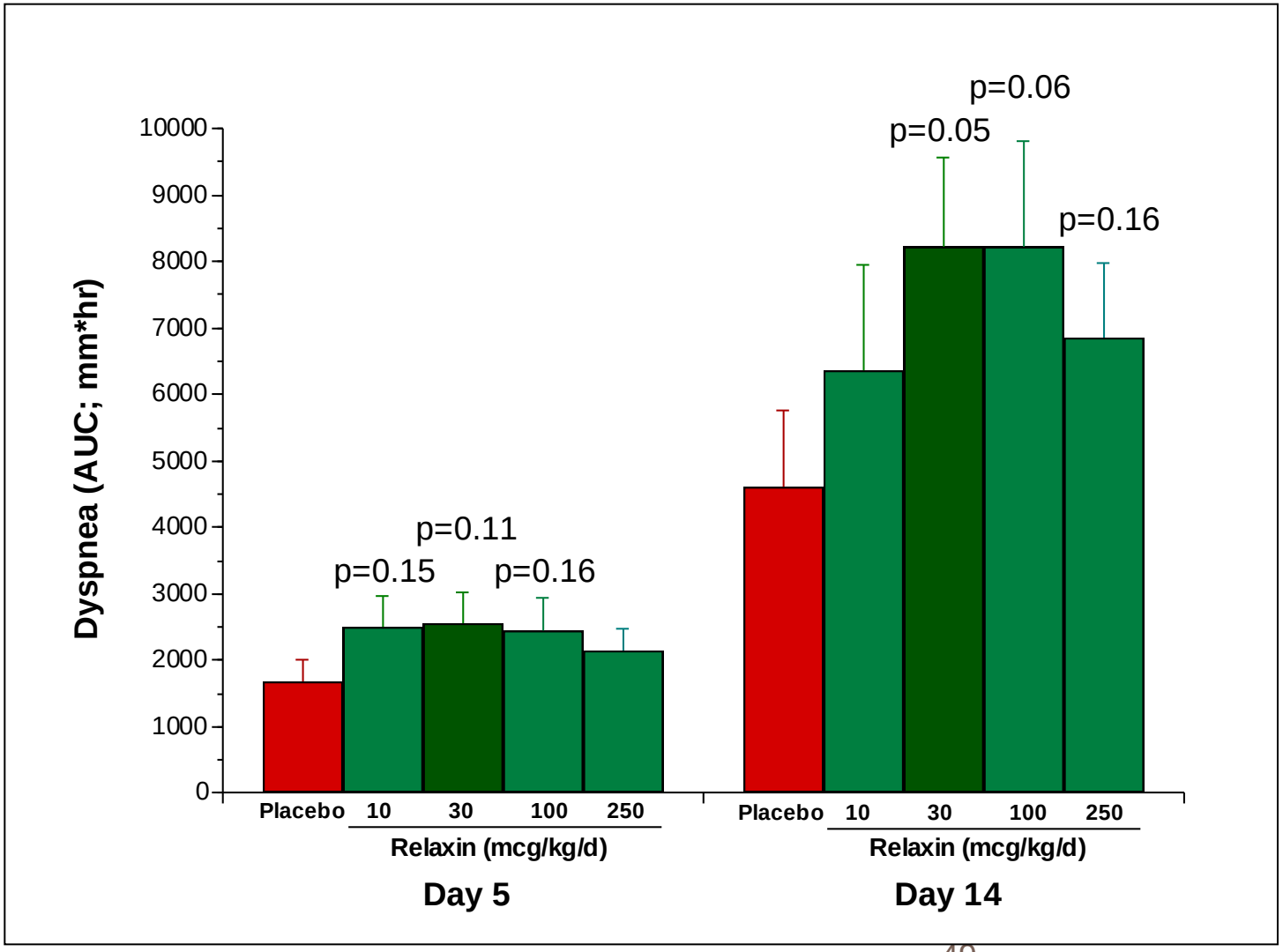
Patient Population

- "Acute Vascular Failure" subset of AHF:
  - Dyspnea requiring hospitalization
  - BNP/NT-pro-BNP > 350/1400 pg/mL
  - Baseline BP > 125 mmHg
  - Renal dysfunction (CrCl 30-75 mL/min)

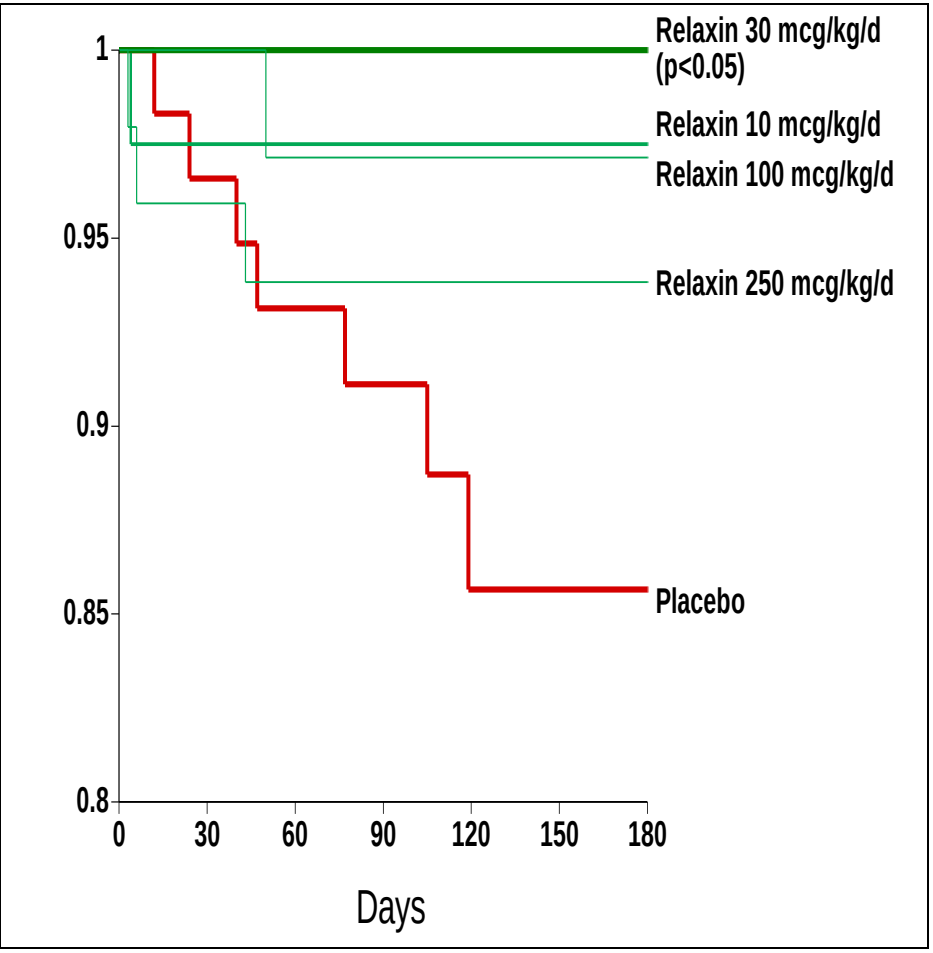
Study Endpoints & Objectives

- Dyspnea (shortness of breath): Serial Likert and VAS to Day 14
- Other AHF measures - Signs, symptoms, outcomes through Day 14 - 180
- Safety, including renal dysfunction
- Choose dose, endpoints, sample size, sites for pivotal P3 trials

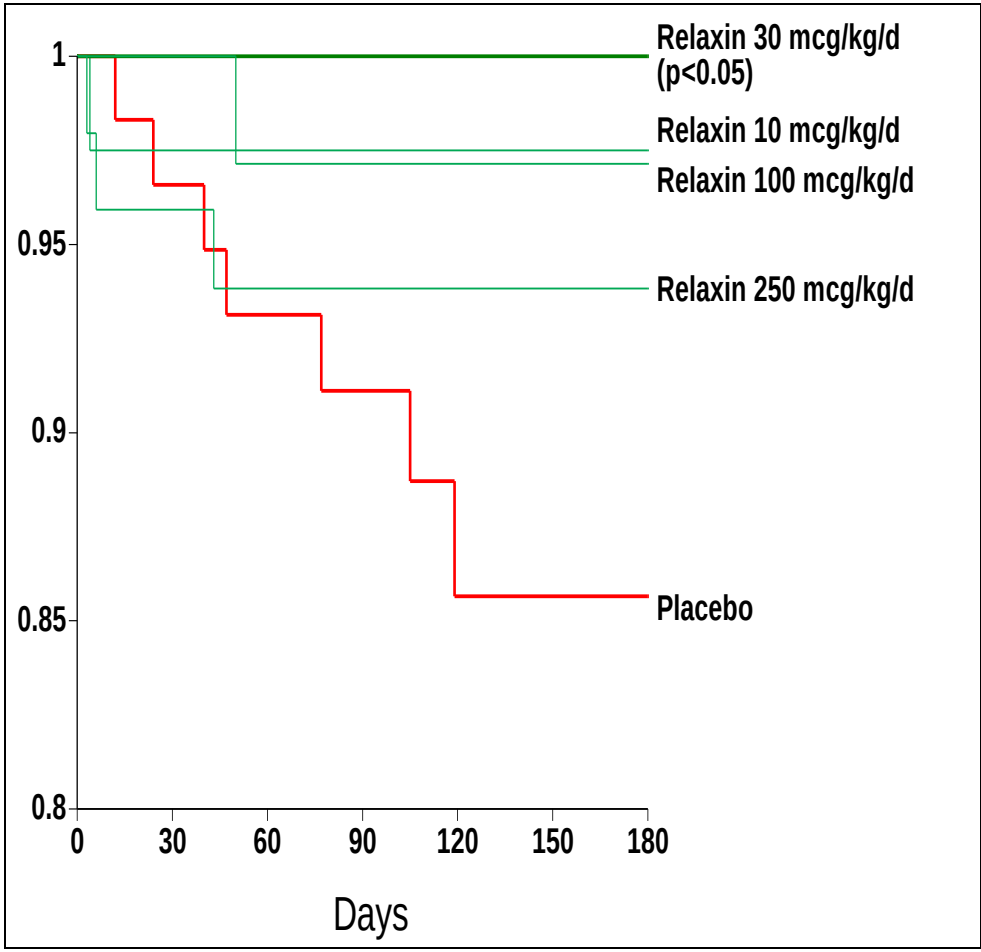
Dyspnea Improvement over Time



CV Death or Heart/Renal Failure Re-hospitalizations to Day 60

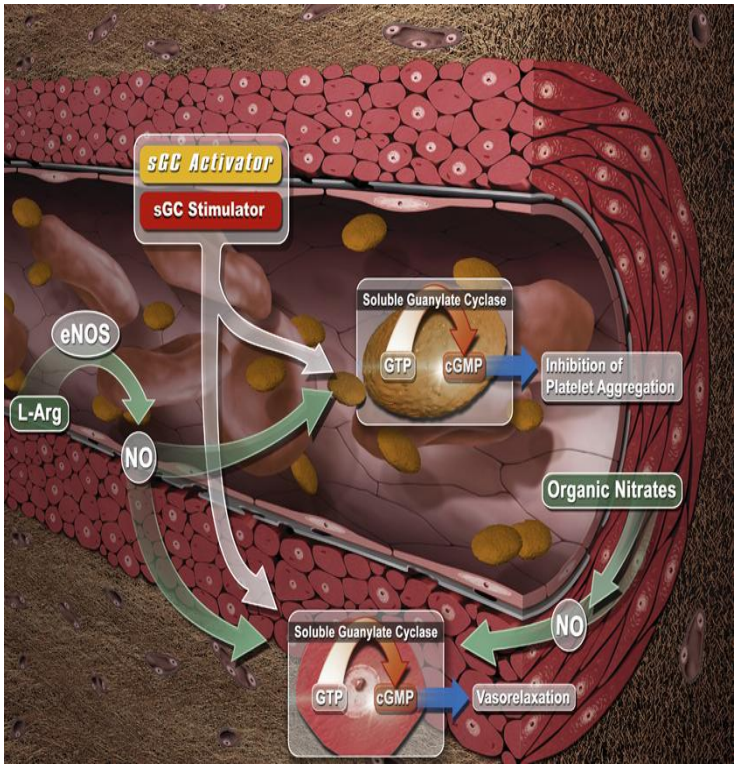


Cardiovascular Deaths to Day 180



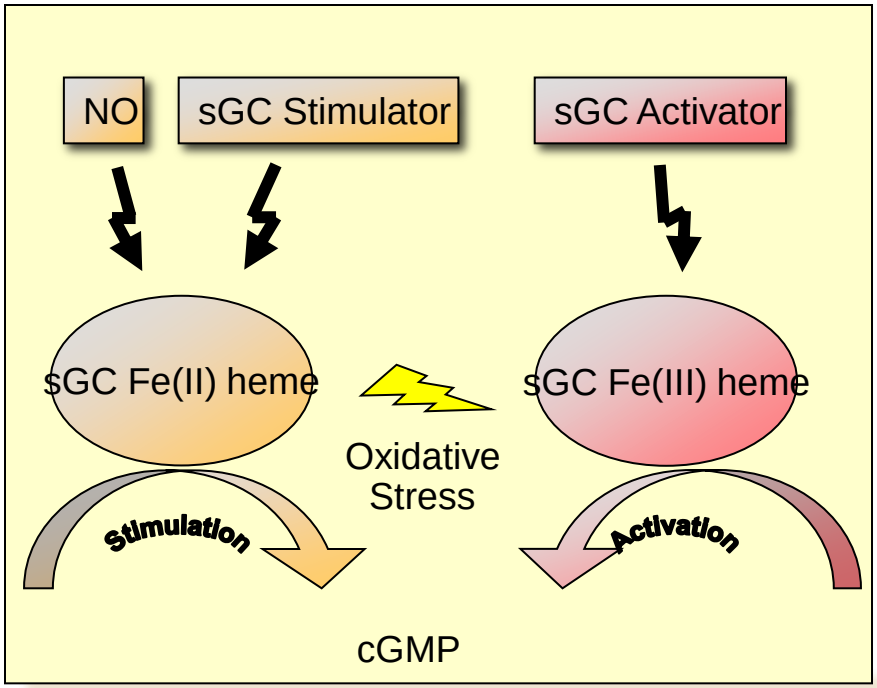
Critical look – Too good to be true? Lack of clear mechanism of action?

soluble Guanylate Cyclase (sGC) Stimulators and sGC Activators



sGC Stimulator

➔ Amplifies protective effects of NO in the cardiovascular system



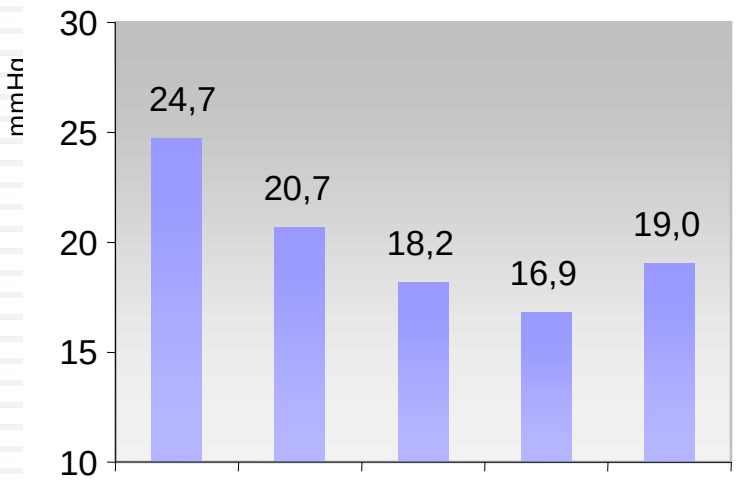
sGC Activator

➔ NO-independent mode of action

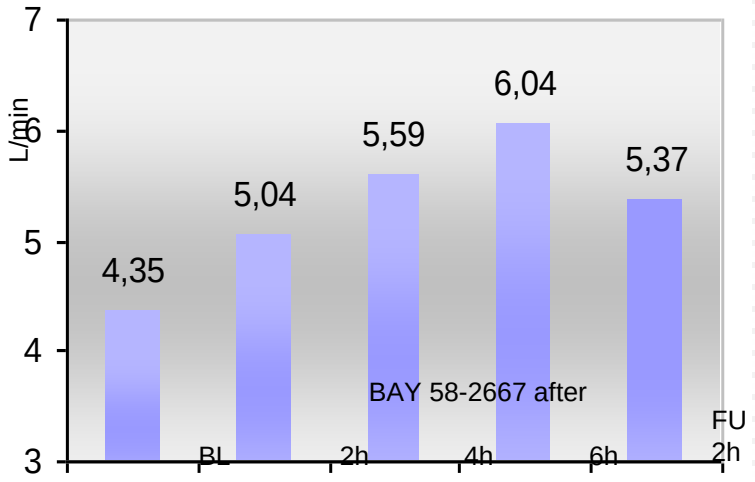
➔ Selective dilation of diseased or oxidative stress impaired blood vessels

Proof of Concept Study – Hemodynamic Results

PCWP



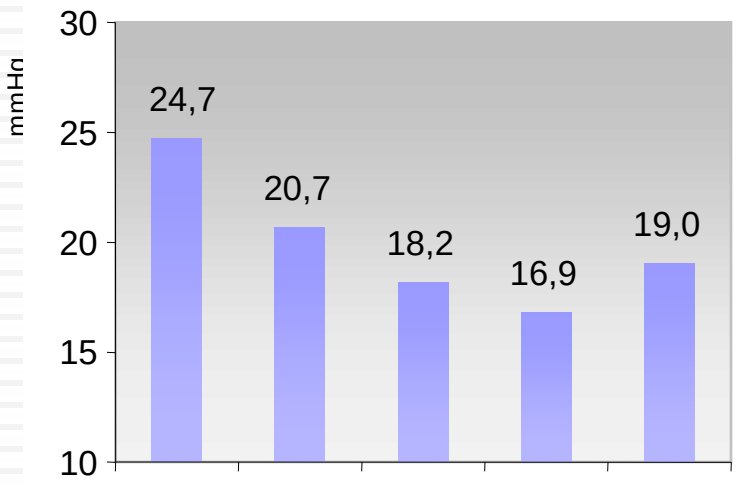
Cardiac Output



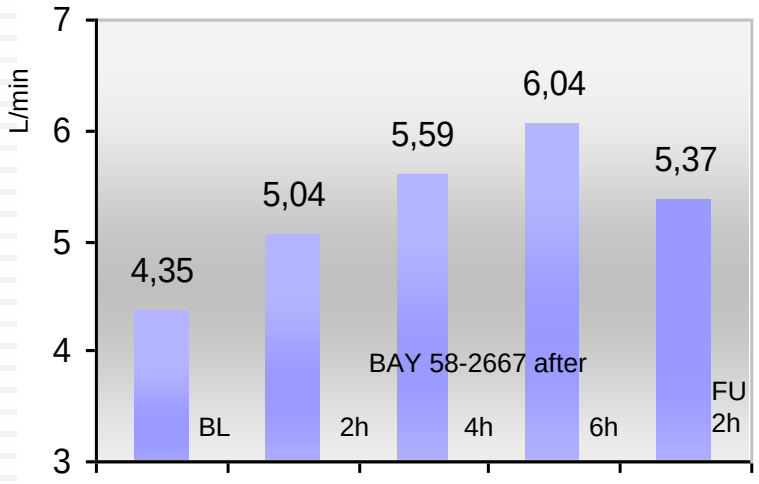
Critical look – (1) may increase risk of hypotension
(2) Will need very careful titration and patient selection, but for some patients especially with endothelial dysfunction – may be very helpful

Proof of Concept Study – Hemodynamic Results

PCWP



Cardiac Output



CONCLUSIONS

Vasodilators may be beneficial in AHF. However, this has never been shown in prospective well-powered studies.

Vasodilators make pts feel bettter

- Can these effects be achieved without collateral damage to vital organs such as kidneys, heart and brain ?
- Can these be achieved without leading to detrimentral effects on readmission or death or even reduce these outcomes ?
- Are all vasodilators equal or are venous vasodilators or renal vasodilators superior ?

AHF AND VASODILATORS

Multiple physiopathological mechanisms

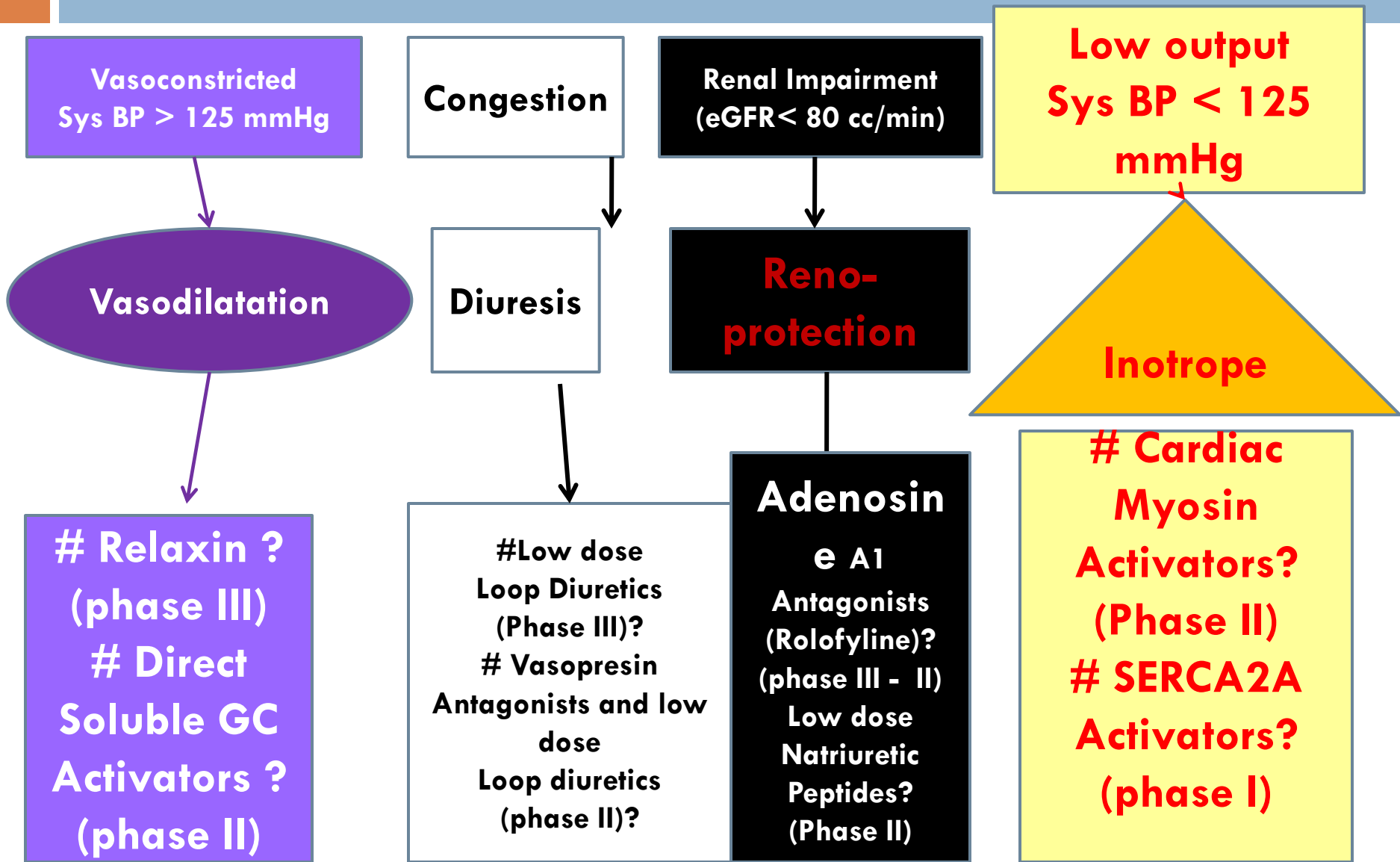
Different clinical presentations / different diseases

Multiple effects of vasodilator therapy

We remain with:

- Nitrates
- Nitroprusside in patients without active ischemia
- Need of other trials and drugs

AHF THERAPY 2013 – COMBINATION THERAPY?



Why trials in AHF have failed ???

1. Patient heterogeneity
   - Substrate (ischaemic / non ischaemic, HT).
   - Trigger (ACS, arrhythmias, Hypertension crisis).
   - Pathophysiology (systolic vs diastolic HF / low vs high BP).
2. Lack of standard comparator.
3. COMPLEXITY ? Endpoints, time points, dose

SIMPLICITY IS THE ULTIMATE SOPHISTICATION.

(LEONARDO DA VINCI)