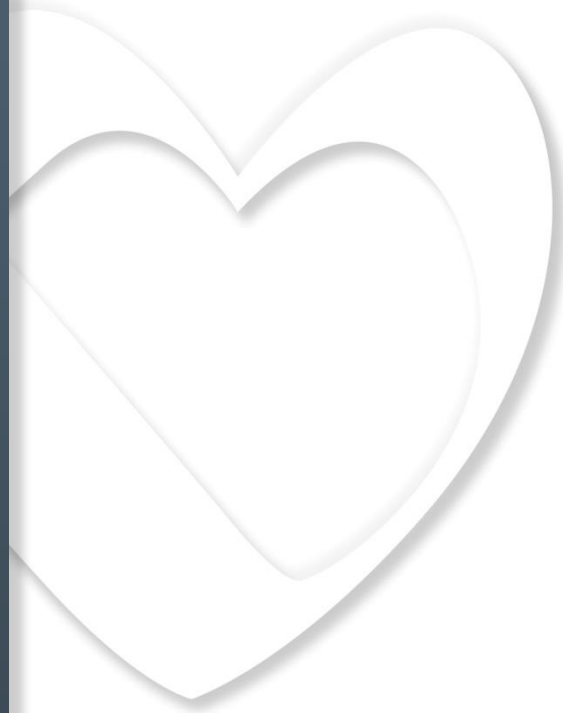
Early Management of Acute Heart Failure: Time is also muscle

Gerasimos Filippatos, MD, FESC, FHFA
Athens, GR



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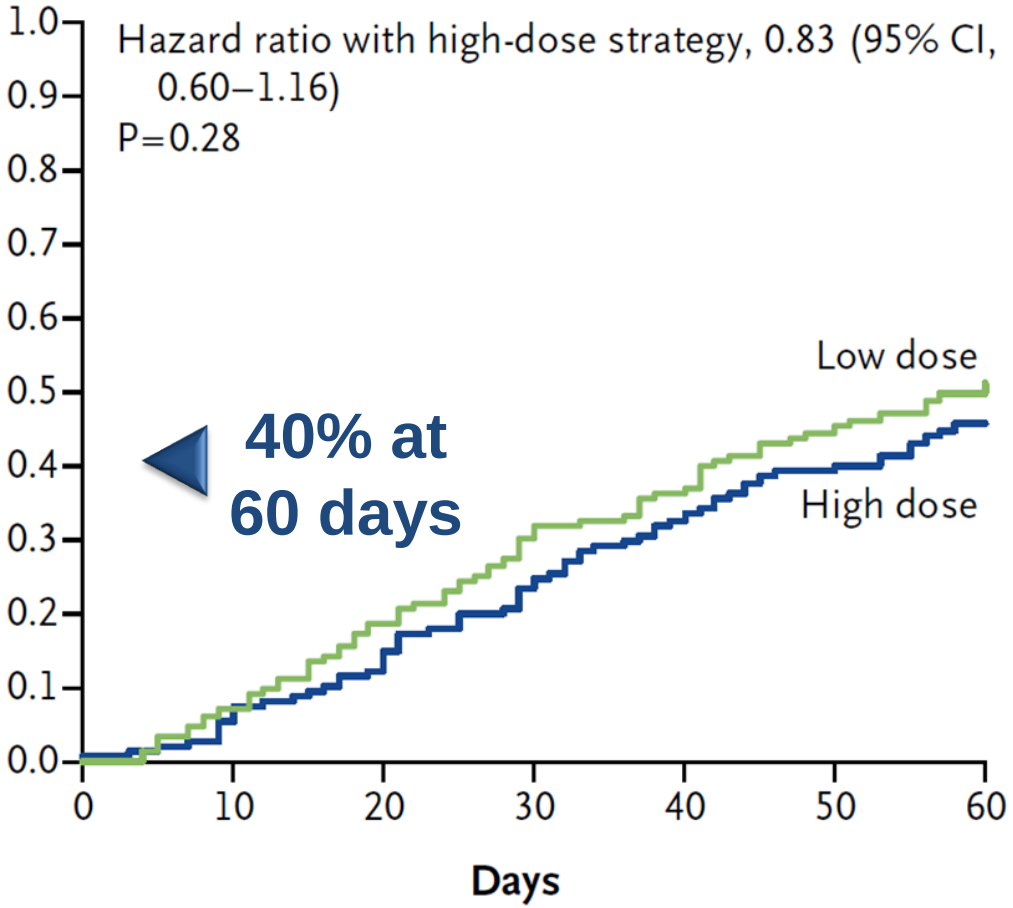
Disclosures

Principal Investigator or Committee member in trials sponsored by Novartis, Bayer, Cardiorentis, Vifor, European Union

Outcome in acute HF is still poor

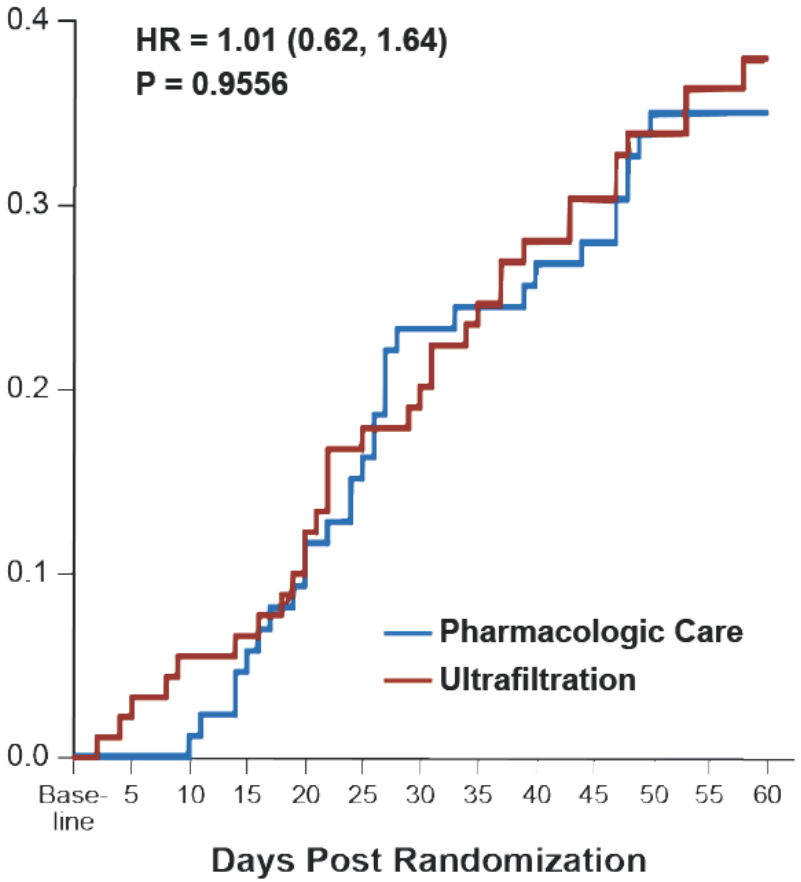
DOSE

Death, Rehospitalization or ER visit



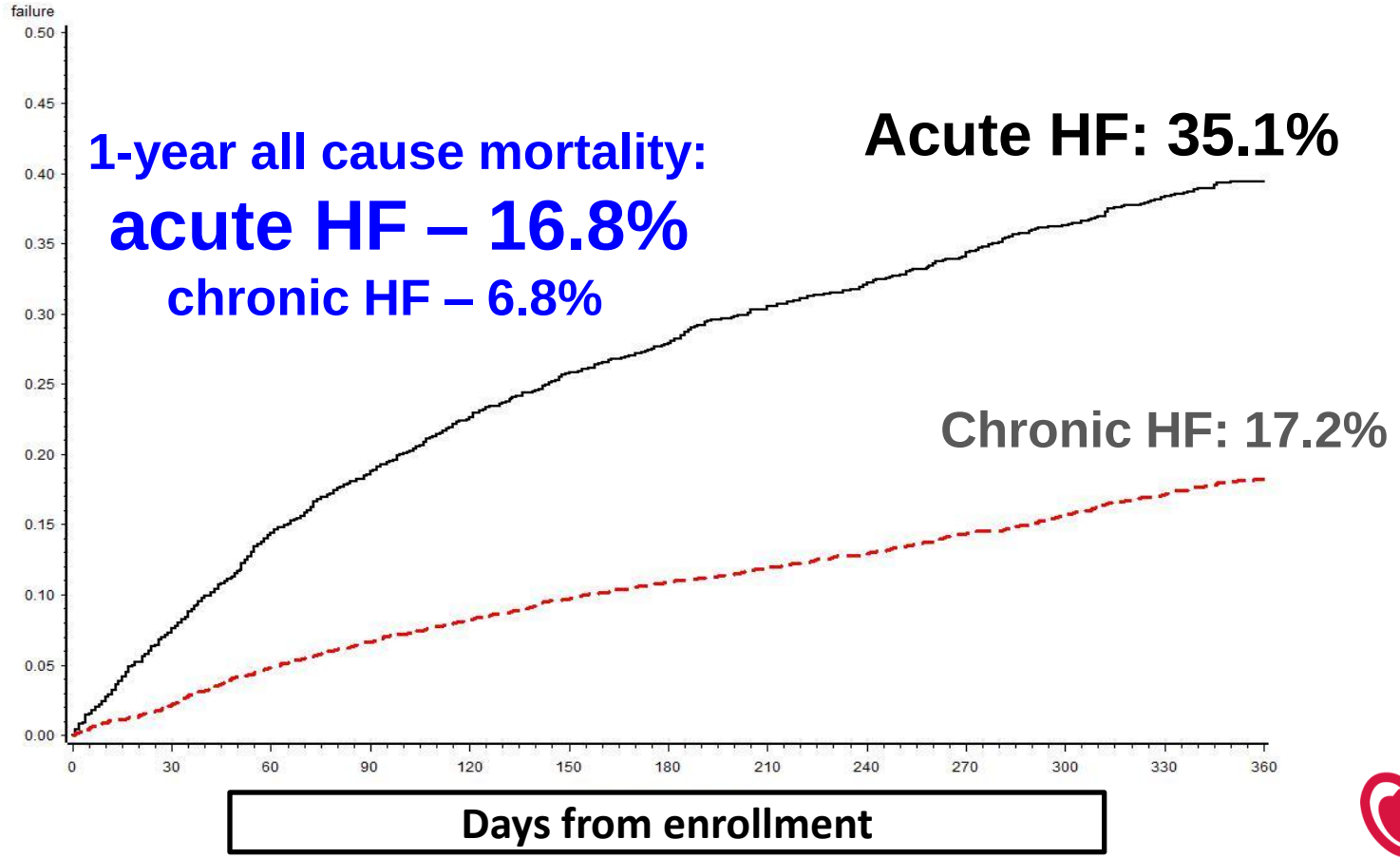
CARRESS-HF

Death or HF Rehospitalization



EUR*Observational* Research Program:
The Heart Failure Pilot Survey

All-cause death or hospitalization



A. Maggioni, U Dahltrom, G, Filippatos et al EJHF2011

Management of acute heart failure: why so difficult ?

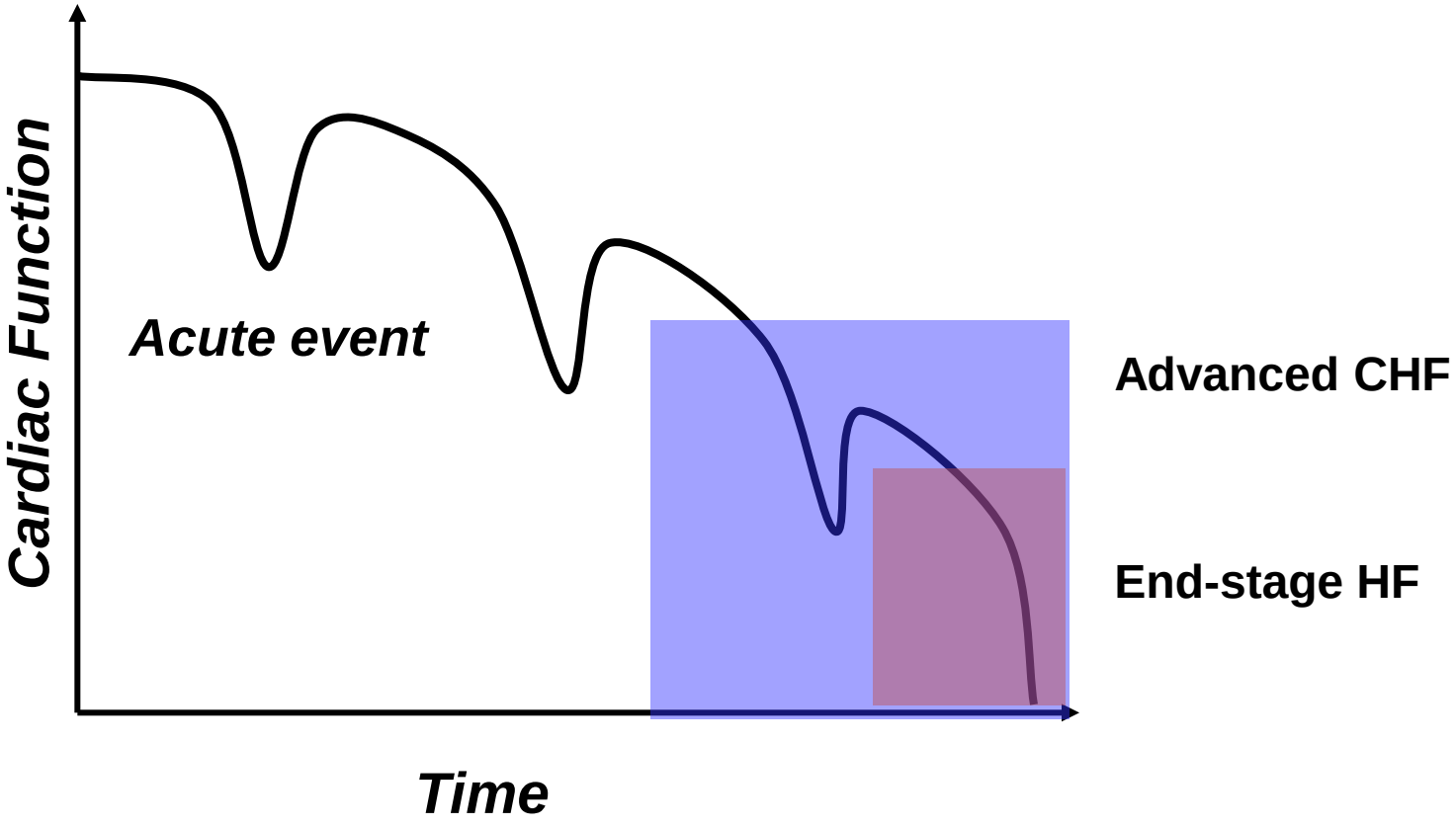
Clinical Factors:

- Underlying causes: multifactorial, precipitating factor often not identified
- Clinical presentation: spectrum of various conditions, heterogeneous pathophysiology
- Cardiovascular and non-cardiovascular comorbidities

Pathophysiological targets: uncertain

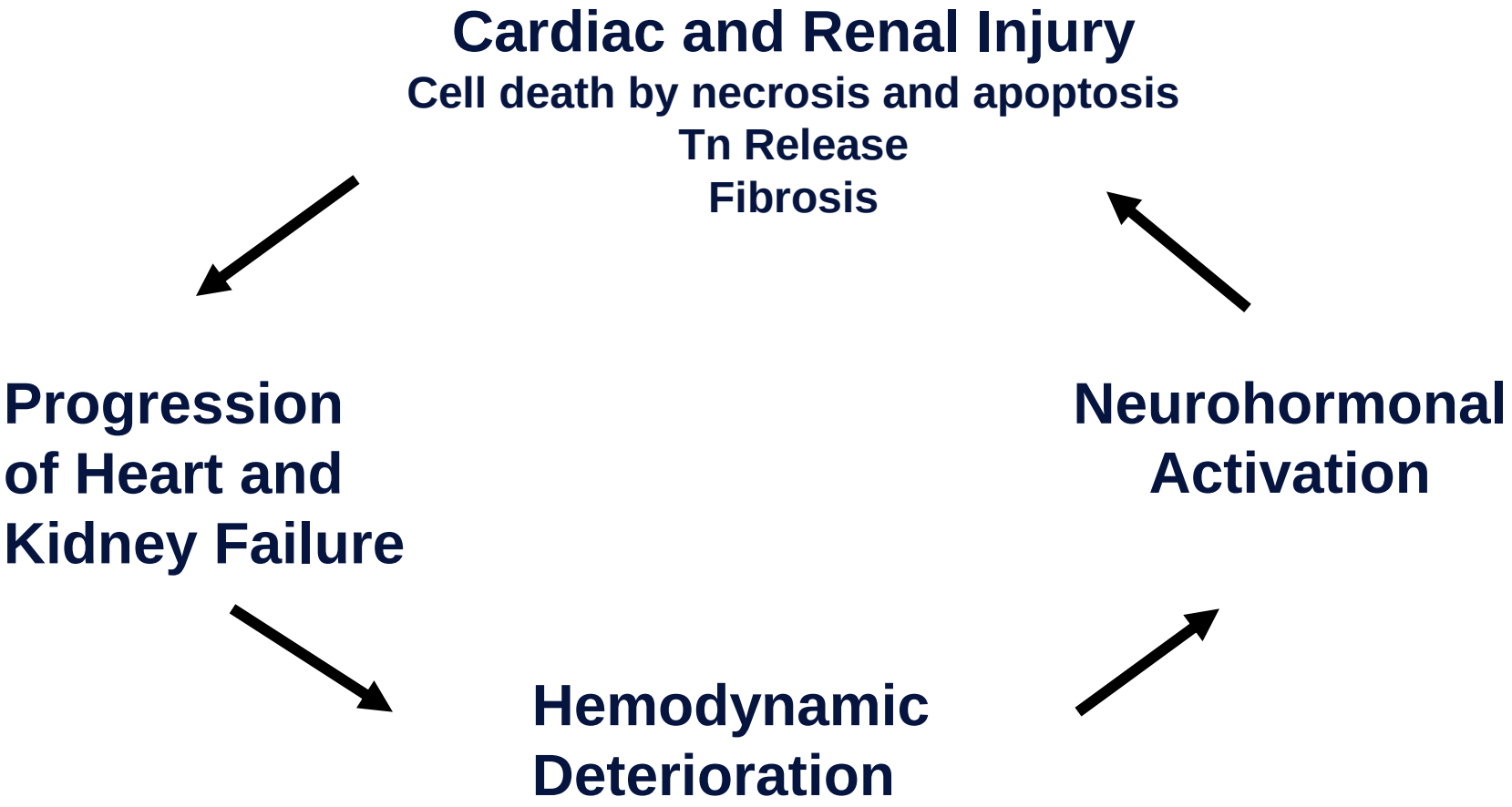
Courtesy of Piotr Ponikowski

Acute Exacerbations May Contribute to the Progression of the Disease



Gheorghiade M, Fonarow G, Metra M, Filippatos G Francis G. Am J Cardiology 2005

MECHANISMS OF DISEASE PROGRESSION



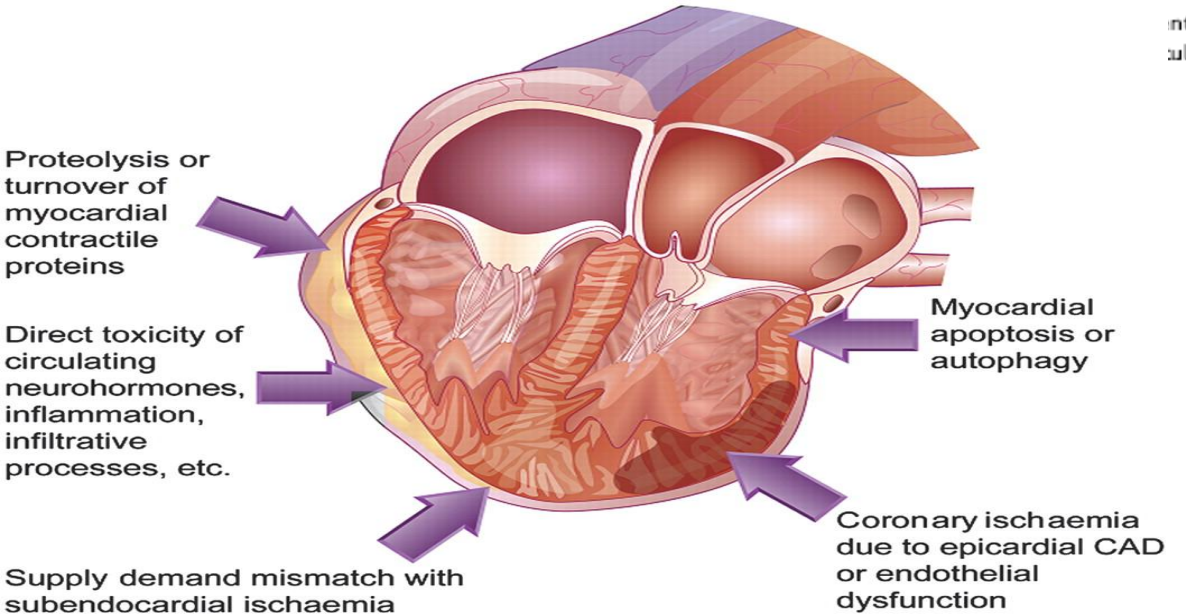
Modified from Filippatos G et al. Am J Physiol 1999

Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: *Heart Failure Section*

James L. Januzzi Jr[1]*, Gerasimos Filippatos[2], Markku Nieminen[3] and Mihai Gheorghiade[4]

[1]Cardiology Division, Mas
Hospital Attikon, Athens,
University Feinberg Schoc

nt of Cardiology, Athens University
ular Innovation, Northwestern



Selected causes of reduced oxygen supply:

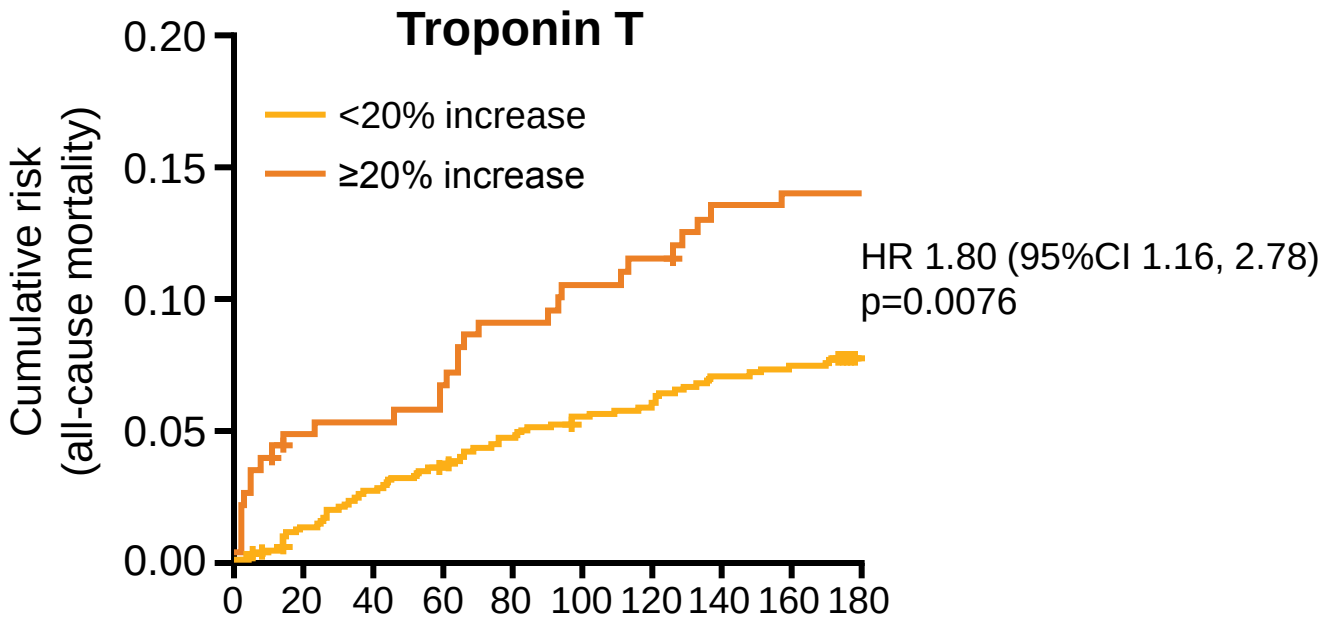
- Anaemia
- Hypotension

Selected causes of increased myocardial oxygen demand:

- Increased transmural wall stress
- Dilated left ventricular chamber size
- Elevated pressures in cardiac chambers
- Left ventricular hypertrophy
- Diastolic stiffening of the myocardium

Increases from baseline in hs-cTnT levels are associated with increased mortality in patients with AHF

- Increased hs-cTnT levels from baseline were associated with increased 180-day mortality
- At Day 2, an increase in hs-cTnT ≥20% over baseline, indicative of substantial additional myocardial necrosis, nearly doubled the risk of mortality through Day 180

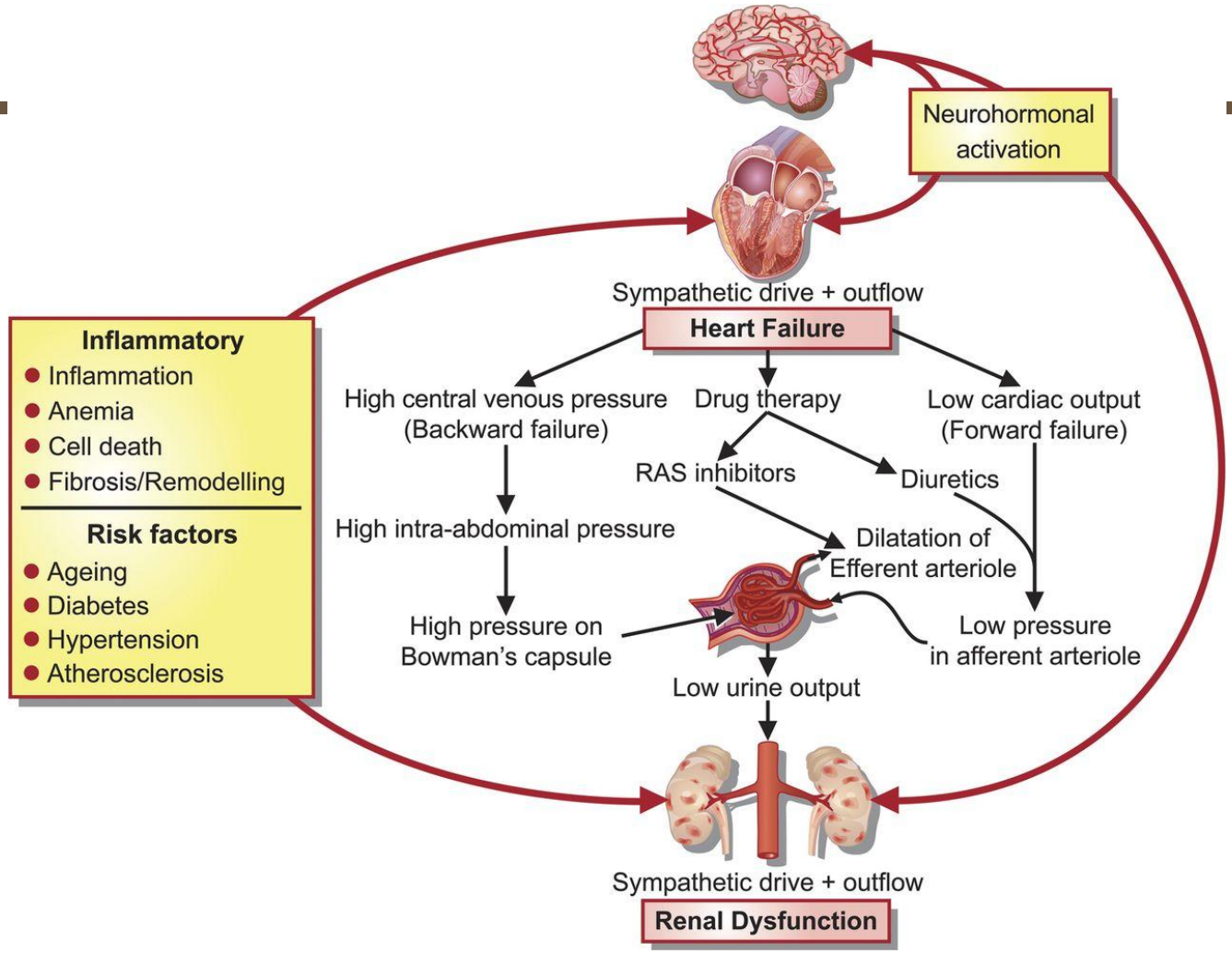


Number at risk:										
<20% increase	825	810	799	790	782	775	771	762	759	654
≥20% increase	231	219	218	216	210	207	204	200	199	174

Data from the RELAXin in Acute Heart Failure (RELAX-AHF study); AHF=acute heart failure; CI=confidence interval; HR=hazard ratio; hs-cTnT=high sensitivity cardiac troponin T; KM=Kaplan-Meier

Metra et al. J Am Coll Cardiol 2013;61:196–206

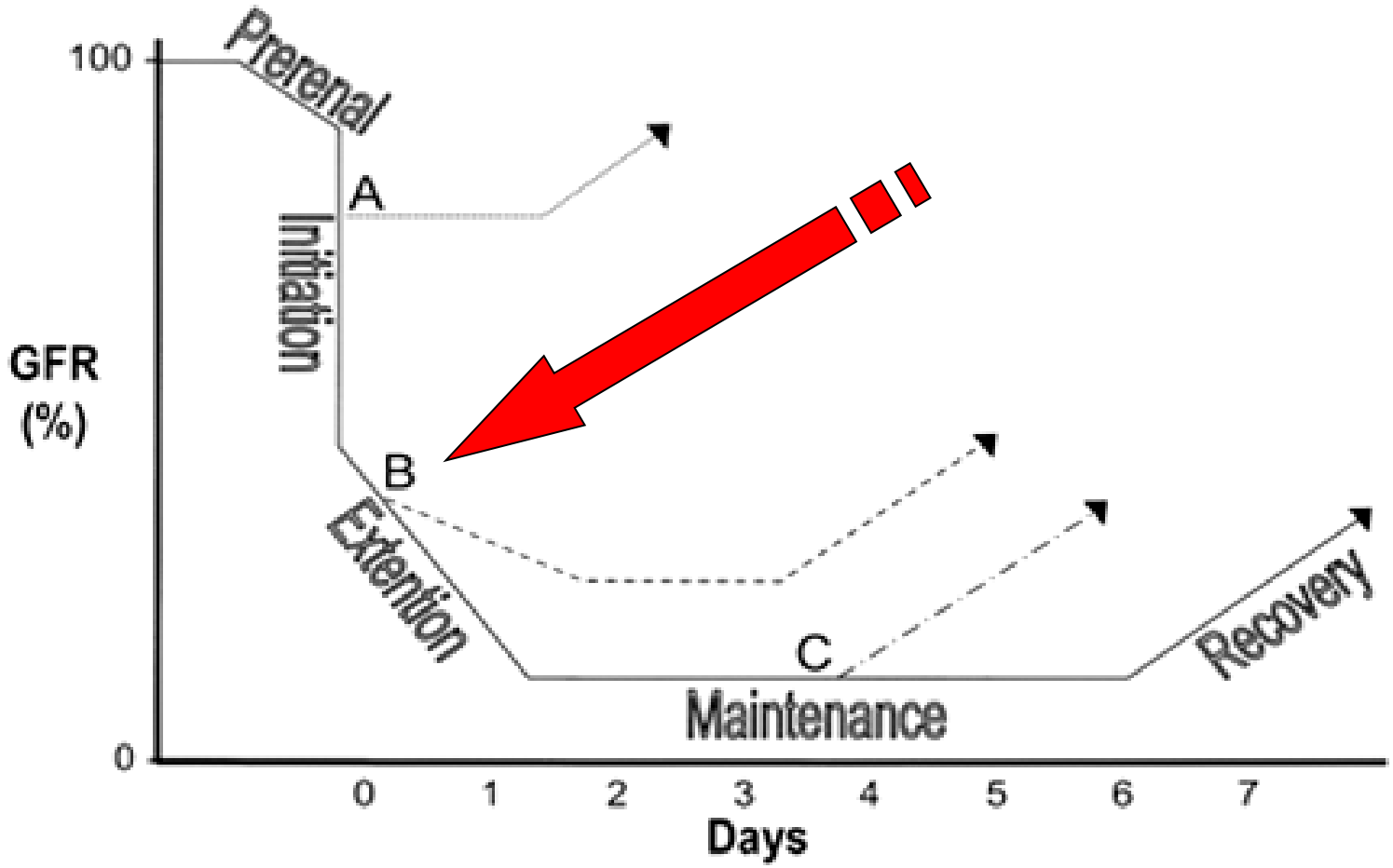
Potential pathogenetic pathways linking heart failure with renal dysfunction.



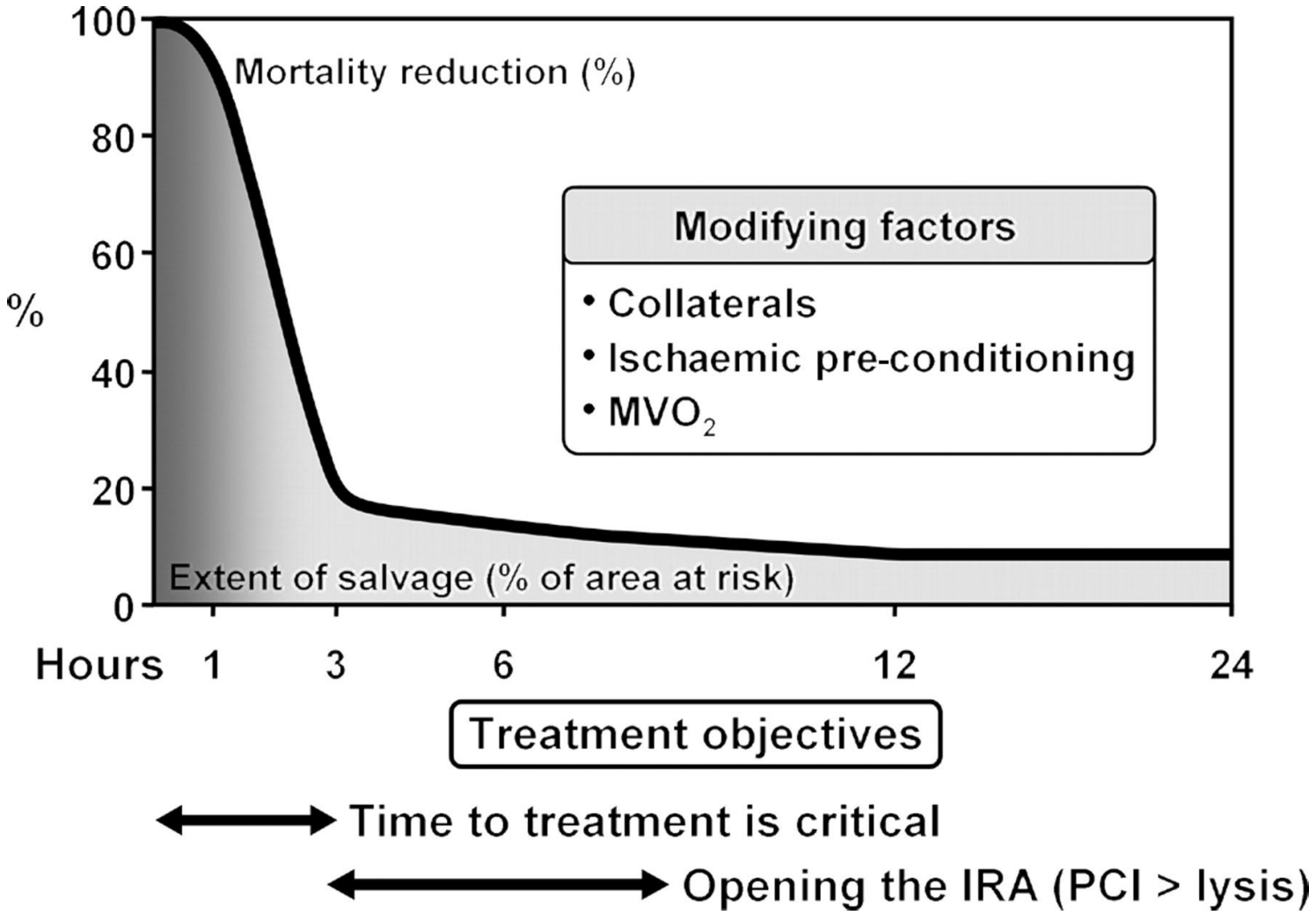
Filippatos G et al. Eur Heart J 2014

European Heart Journal

Acute Kidney Injury Timeline



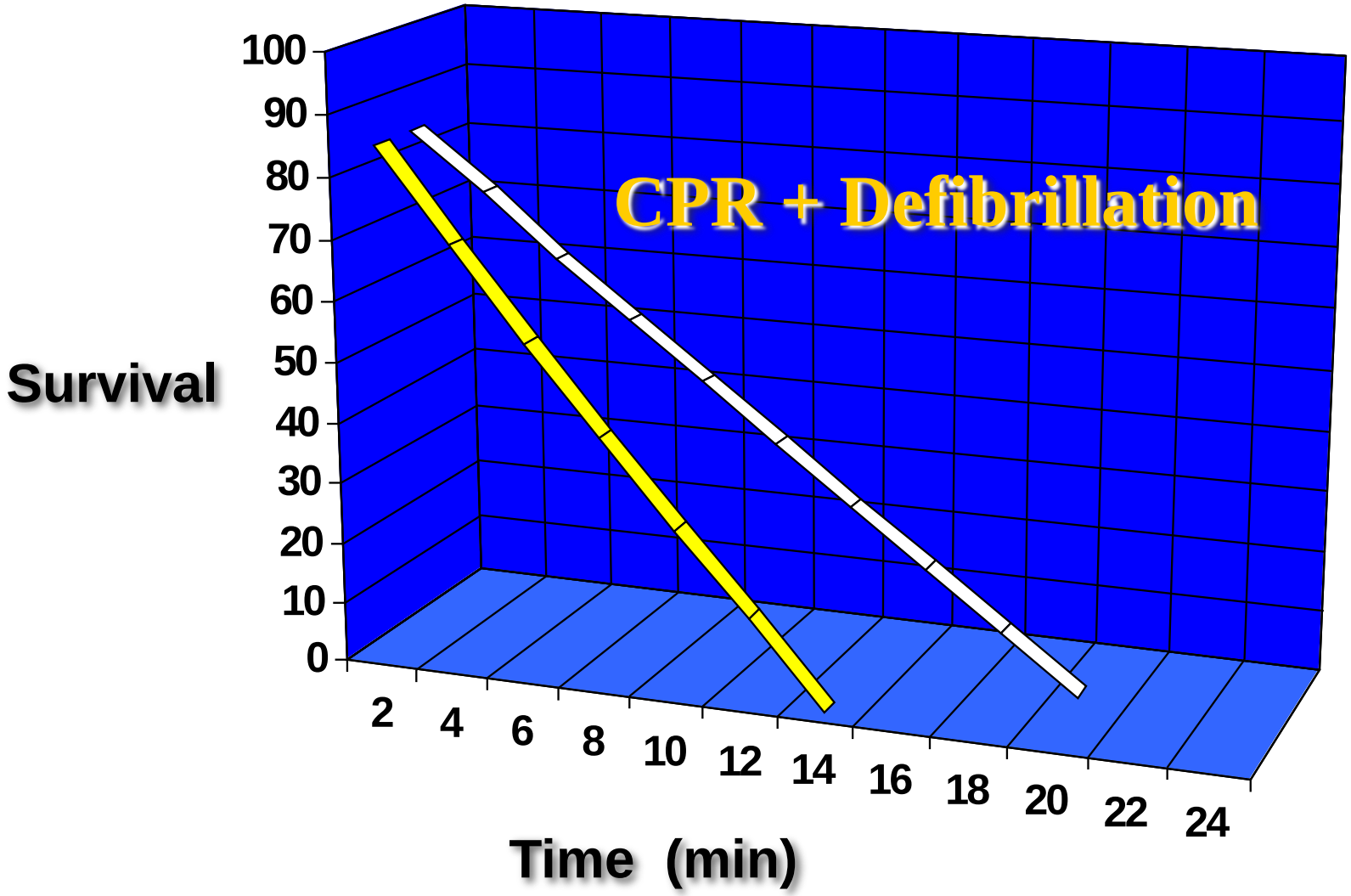
Relationship between time to treatment and the reduction in mortality and extent of salvage.



Gersh B J , and Antman E M Eur Heart J 2006;27:761-763

European Heart Journal

Survival after Cardiac Arrest



The Surviving Sepsis Campaign Resuscitation Bundle

Measure serum lactate

Obtain blood cultures prior to antibiotic administration

From the time of presentation, broad-spectrum antibiotics to be given within 1 h

Source of infection to be identified and drained within 6 h

In the event of hypotension and/or lactate >4 mmol/L (36 mg/dL):

- deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
- give vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure ≥65 mmHg

In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate >4 mmol/L (36 mg/dL):

- achieve central venous pressure of ≥8 mmHg
- achieve central venous oxygen saturation of ≥70%

Daniels R J. Antimicrob. Chemother. 2011;66:ii11-ii23

Journal of Antimicrobial Chemotherapy

Goals of Treatment in Acute Heart Failure

- Treat symptoms
- Restore oxygenation
- Improve organ perfusion & haemodynamics
- Limit cardiac/renal damage
- Prevent thrombo-embolism
- Minimize ICU length of stay

Immediate (ED/ICU/CCU)

- Stabilise patient and optimise treatment strategy
- Initiate and up-titrate disease-modifying pharmacological therapy
- Consider device therapy in appropriate patients
- Identify aetiology and relevant co-morbidities

Intermediate (in-hospital)

- Plan follow-up strategy
- Enrol in disease management programme, educate, initiate appropriate lifestyle adjustments
- Plan to up-titrate/optimize disease-modifying drugs
- Assess for appropriate device therapy
- Prevent early readmission
- Improve symptoms, quality of life and survival

Long-term and pre-discharge management

Phases in the AHF management

ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012

Recommendations for the treatment of acute heart failure in HFA – ESC 2012 guidelines

Recommendations	Class[a]	Level[b]
Patients with pulmonary congestion/oedema without shock		
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B
High-flow oxygen is recommended in patients with a capillary oxygen saturation <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C
Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	A
Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate >20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure <85 mmHg (and blood pressure should be monitored regularly when this treatment is used).	IIa	B
An i.v. opiate (along with an antiemetic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.	IIa	C
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B
Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C

Acute Heart Failure management

Pharmacological therapy

1. Acute management

Oxygen
Diuretics
Opiates
Vasodilators
Nesiritide
Inotropes
Vasopressors

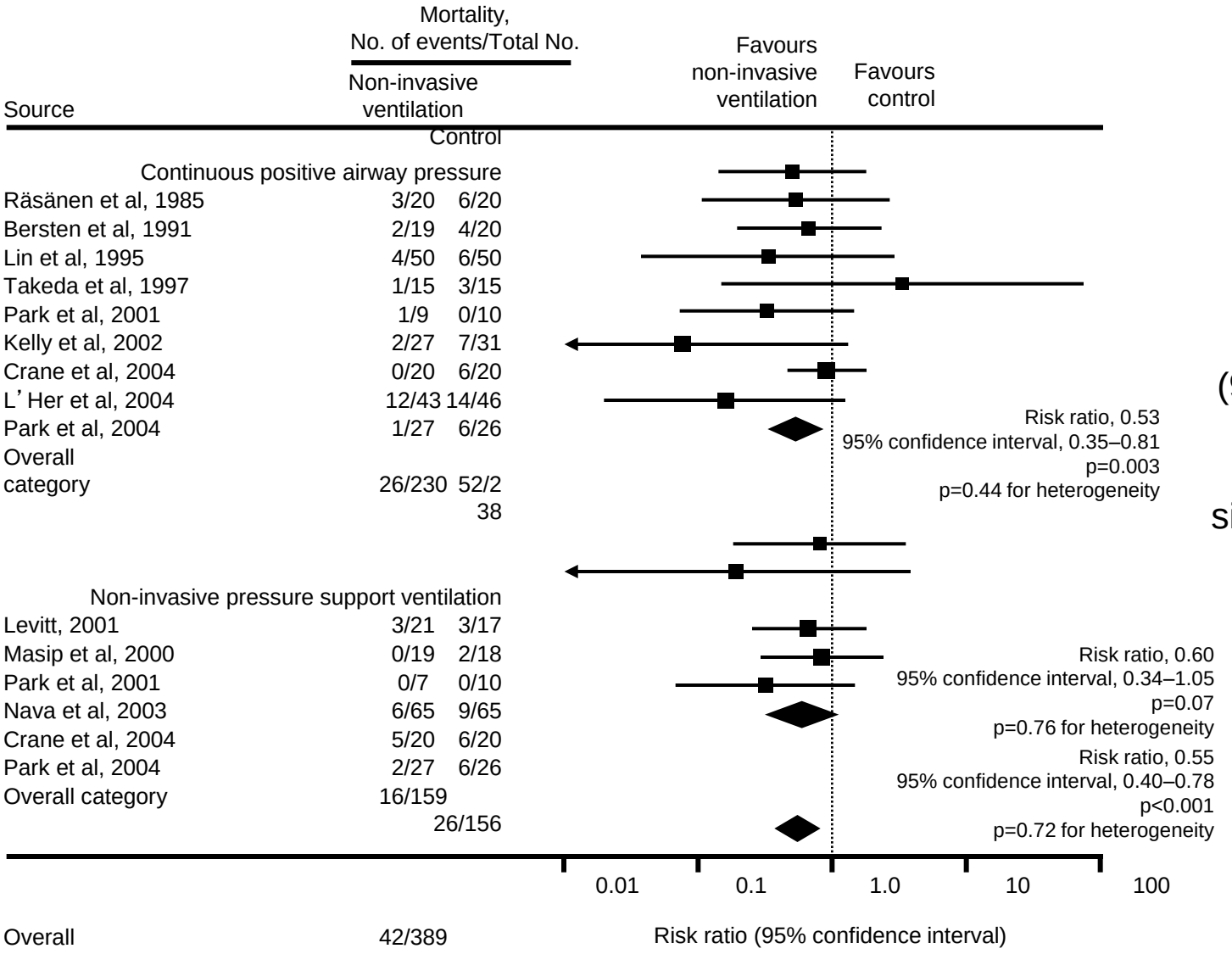
2. After stabilization

ACE inhibitor / ARB
Beta-blocker
Mineralocorticoid receptor antagonist
Digoxin

Non-pharmacological therapy

1. **Sodium and fluid intake restriction**
2. **Ventilation**
   non-invasive
   invasive
3. **Mechanical circulatory support**
   IABP
   VAD
4. **Ultrafiltration**

Mortality benefit of CPAP/NIPPV in patients with ACPO



Mortality reduced from 22% to 11%

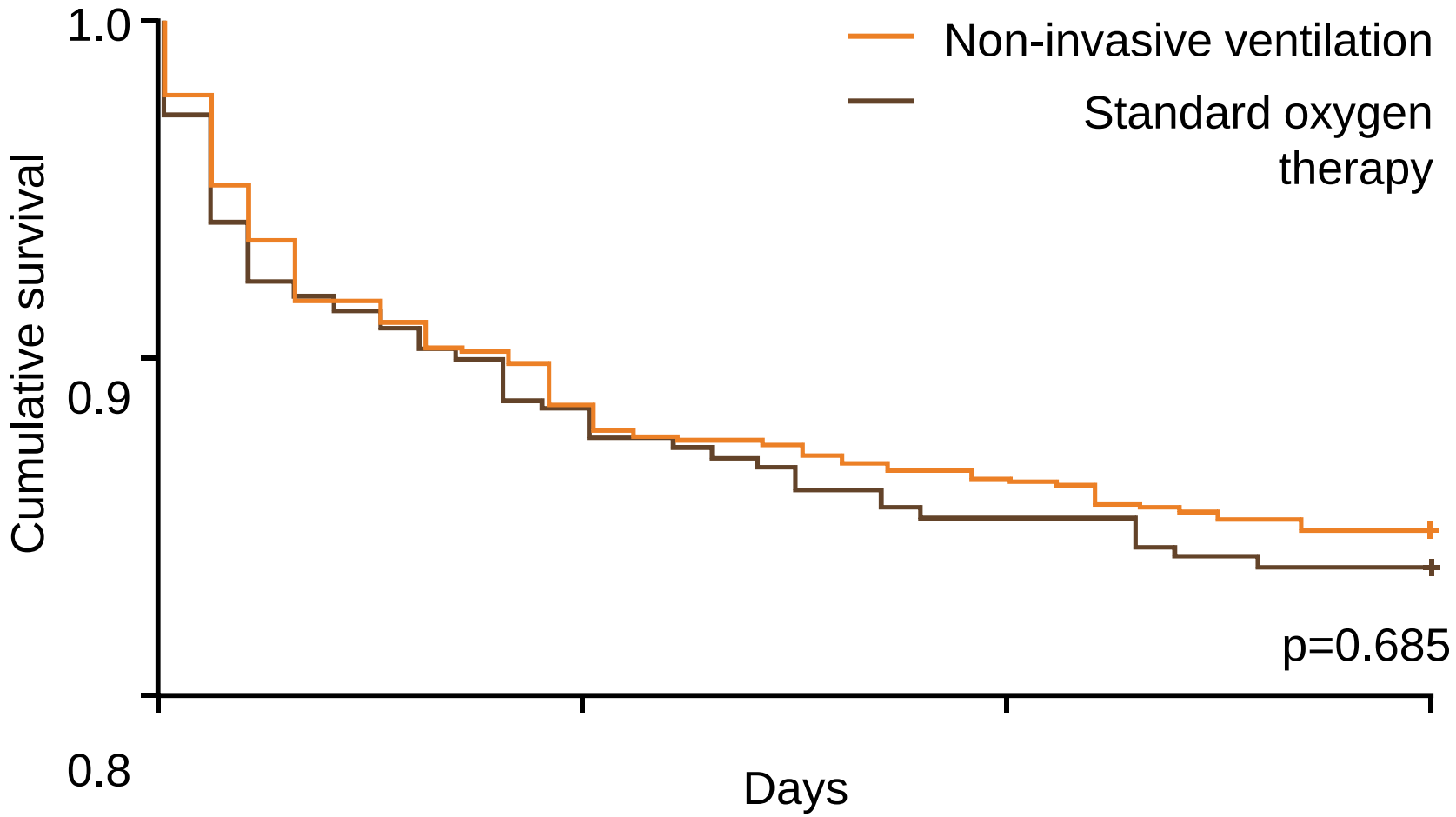
RR 0.53
(95% CI 0.35-0.81)

(Individual group sizes of n = 9 to 46)

Masip J, et al. JAMA 2005;294:3124–30

Primary outcome: Mortality

Standard oxygen therapy versus non-invasive ventilation



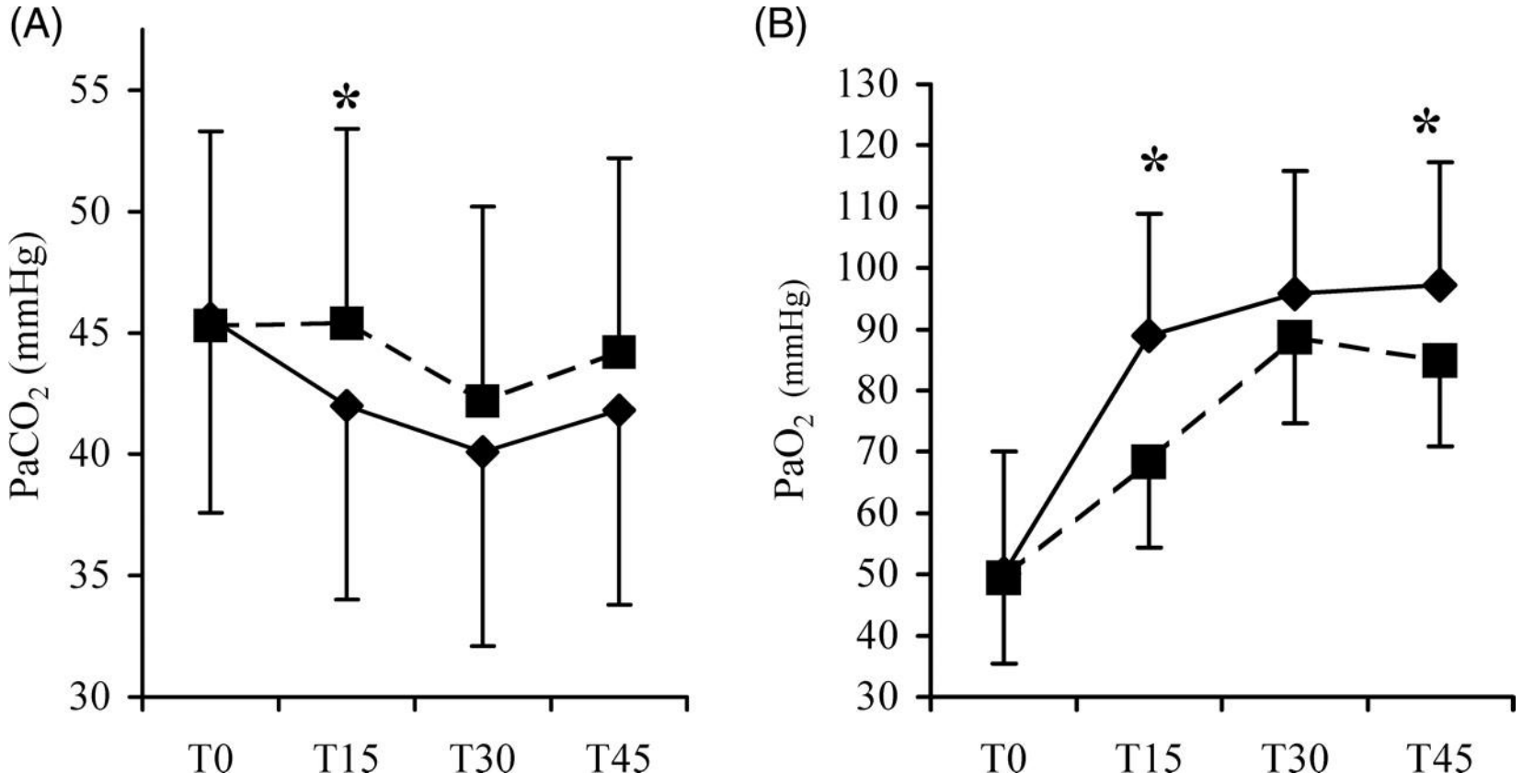
Non-invasive ventilation in ACPO

Comparison of overall mortality and intubation rates in the 3CPO trial and a previous meta-analysis

Variable	3CPO, 7-day rate (N=1069)	Meta-analysis, in-hospital rate (N=783)
	% of patients	
Mortality	9.6	15.3
Intubation	2.9	21.9

Masip J, Mebazaa A, Filippatos G. N Engl J Med 2008;359:2068–9

A randomized study of out-of-hospital continuous positive airway pressure for acute cardiogenic pulmonary oedema: physiological and clinical effects



(A) PaCO2 arterial carbon dioxide tension evolution and (B) PaO2 arterial oxygen tension evolution.

Plaisance P et al. Eur Heart J 2007;28:2895-2901

European Heart Journal

Interventions to Relieve Congestion

- Sodium & fluid restriction
- Diuretics*
- Vasodilators
- Ultrafiltration / dialysis

  - BNP (nesiritide)
  - Vasopressin antagonists

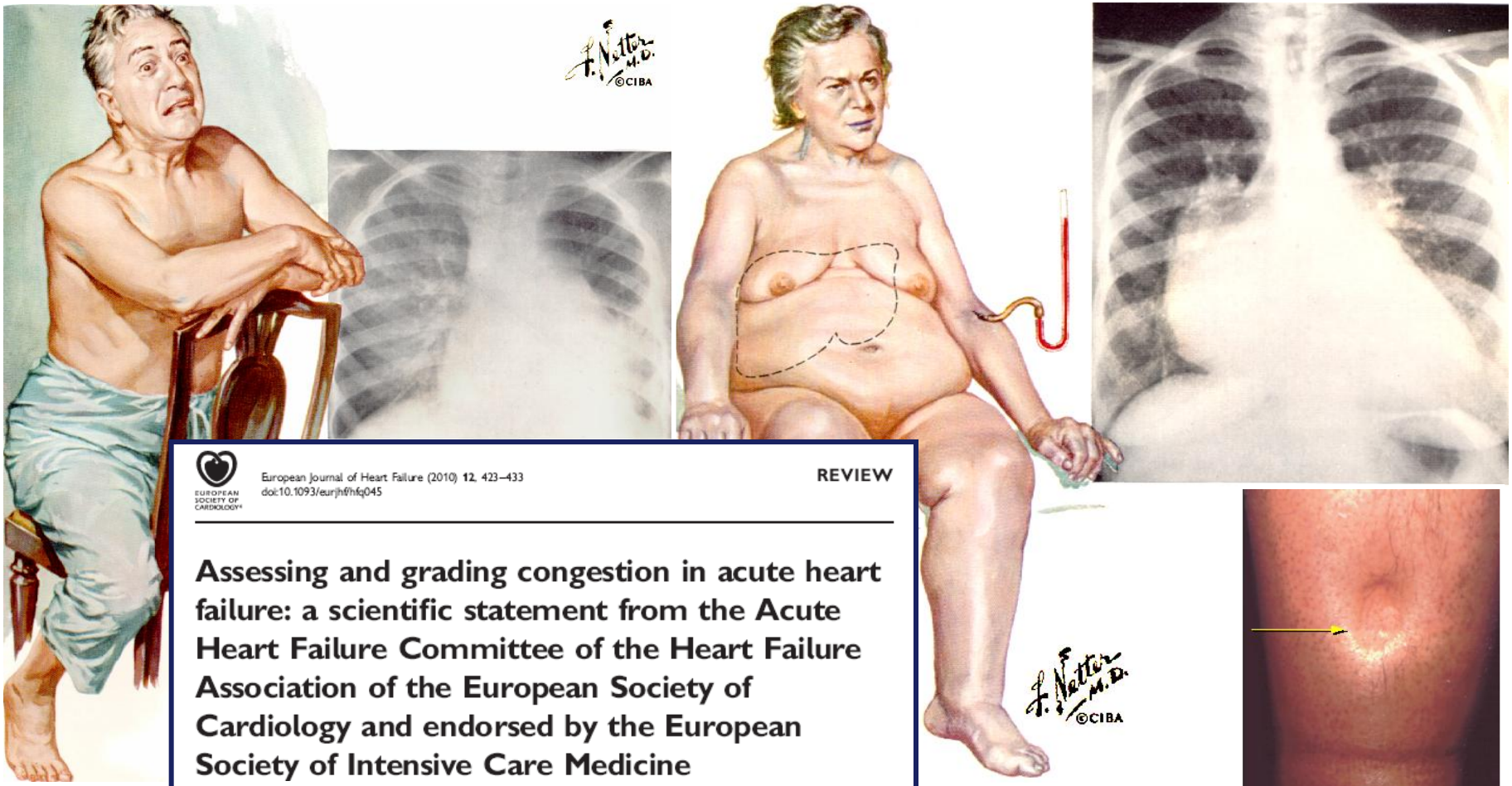
Patients with pulmonary congestion/oedema without shock		
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B

ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012

Congestion in Acute Heart Failure Syndromes: An Essential Target of Evaluation and Treatment

Mihai Gheorghiade, MD,[a] Gerasimos Filippatos, MD,[b] Leonardo De Luca, MD,[c] and John Burnett, MD[d]

The American Journal of Medicine (2006) Vol 119 (12A), S3–S10



European Journal of Heart Failure (2010) 12, 423–433
doi:10.1093/eurjhf/hfq045

REVIEW

Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine

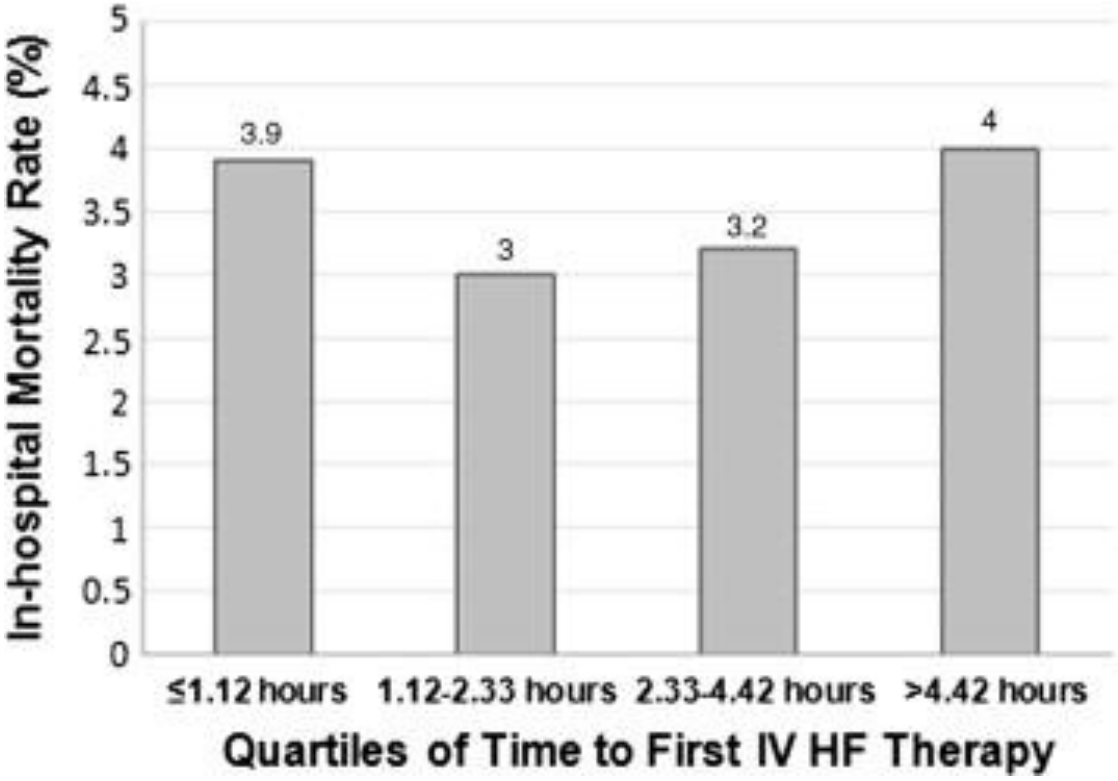
Decompensated chronic HF

- **Consider higher dose of diuretics in renal dysfunction or with chronic diuretic use.**

Diuretics in Hospitalized Patients

If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion.

Early intravenous heart failure therapy and outcomes among older patients hospitalized for AHF: Findings from the ADHERE-EM



Observed in-hospital mortality rate by quartile of time to treatment.

Every hour delay in treatment was associated with a modest increased risk of in-hospital mortality (adjusted OR 1.01; 95% CI 1.00-1.02; P = .001) and an approximately 1.4-hour increase in index admission length of stay (P < .001).

American Heart Journal, Volume 166, Issue 2, 2013, 349 - 356

Patients with pulmonary congestion/oedema without shock		
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B

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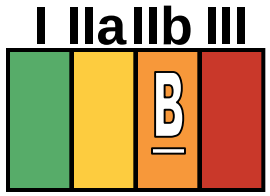


If symptomatic hypotension is absent, intravenous nitroglycerin, nitroprusside or nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF.

ASCEND: Symptoms and Clinical Outcomes by Time to Start Therapy

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure

Post hoc ASCEND-HF analysis: Symptom and clinical outcomes by time to start of therapy

End point	Treatment started <15.5 h, n=3493	Treatment started >15.5 h, n=3514
% with marked improvement in		
Dyspnea at 6 h	16	12
Dyspnea at 24 h	32	25
"Well-being" at 6 h	15	10
"Well-being" at 24 h	28	24
Clinical events at 30 days (%)		
Death	3.5	4.2
Death/HF hospitalization	8.5	11.0
Death/all-cause hospitalization	13.4	17.0

Christopher M O'Connor, ESC-HFA Hotline

TRUE-AHF

TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure

The first-ever acute heart failure (AHF) Phase III trial to be specifically designed to assess the effect of early treatment on cardiovascular mortality as a co-primary endpoint.

Study aim

- efficacy and safety of ularitide on clinical status and mortality in AHF
- build on the growing body of evidence to treat AHF patients as early as possible

RELAX-AHF

THE LANCET

Published online 06.November, 2012

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

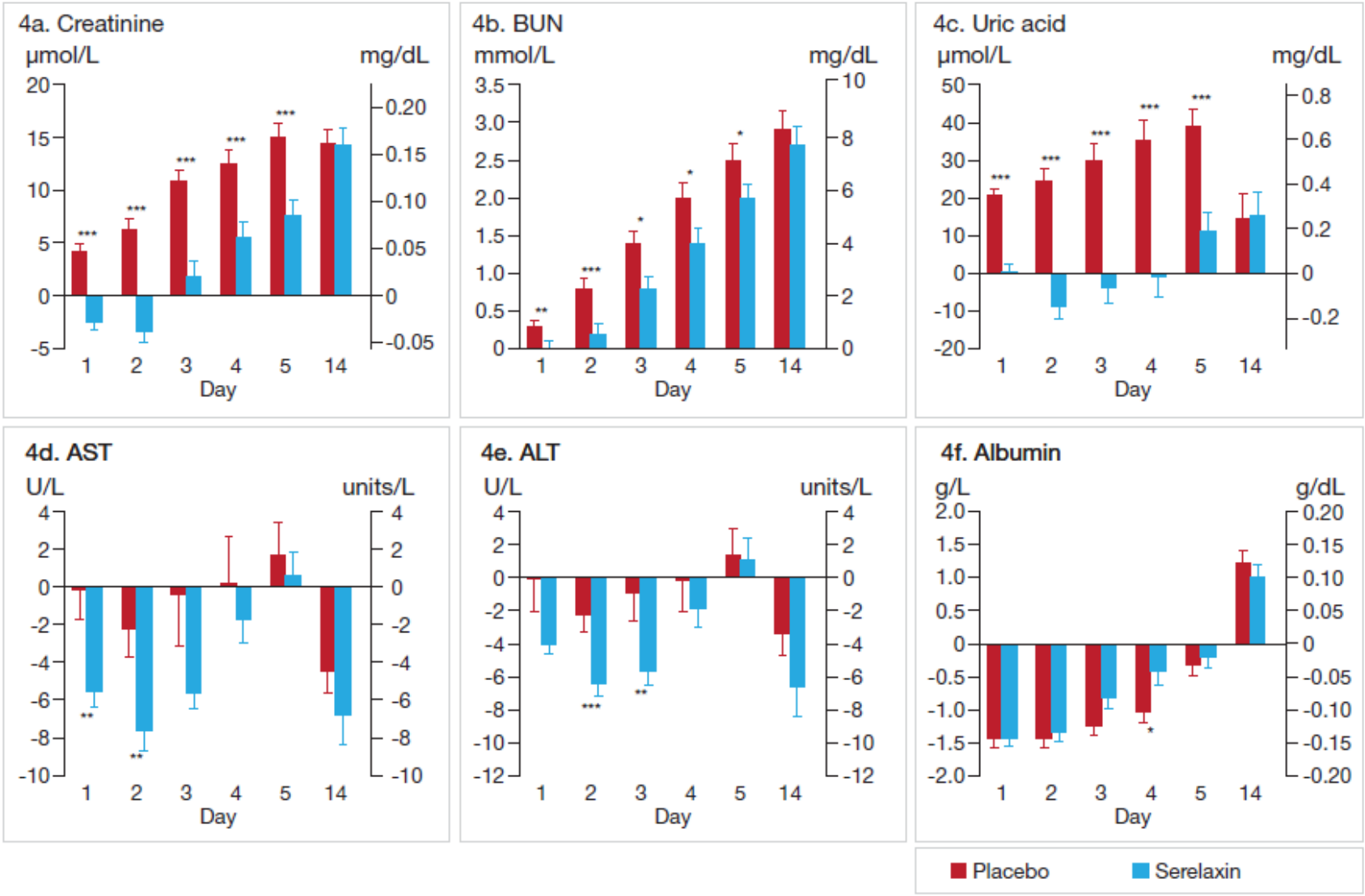
John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Effect of Serelaxin on Cardiac, Renal and Hepatic Biomarkers in the RELAX-AHF Development Program: Correlation with Outcome

Marco Metra, MD; Gad Cotter, MD; Beth A. Davison, PhD; G. Michael Felker, MD, MHS; Gerasimos Filippatos, MD; Barry H. Greenberg, MD; Piotr Ponikowski, MD, PhD; Elaine Unemori, PhD; Adriaan A. Voors, MD, PhD; Kirkwood F. Adams, Jr., MD; Maria Dorobantu, MD; Liliana Grinfeld, MD; Guillaume Jondeau, MD; Alon Marmor, MD; Josep Masip, MD; Peter S. Pang, MD; Karl Werdan, MD; Margaret F. Prescott, PhD; Christopher Edwards; Samuel L. Teichman, MD; Angelo Trapani, PhD; Christopher A. Bush, PhD; Rajnish Saini, MD; Christoph Schumacher, PhD; Thomas Severin, MD; John R. Teerlink, MD; for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

***J Am Coll Cardiol* 2013**

Organ Damage Hypothesis

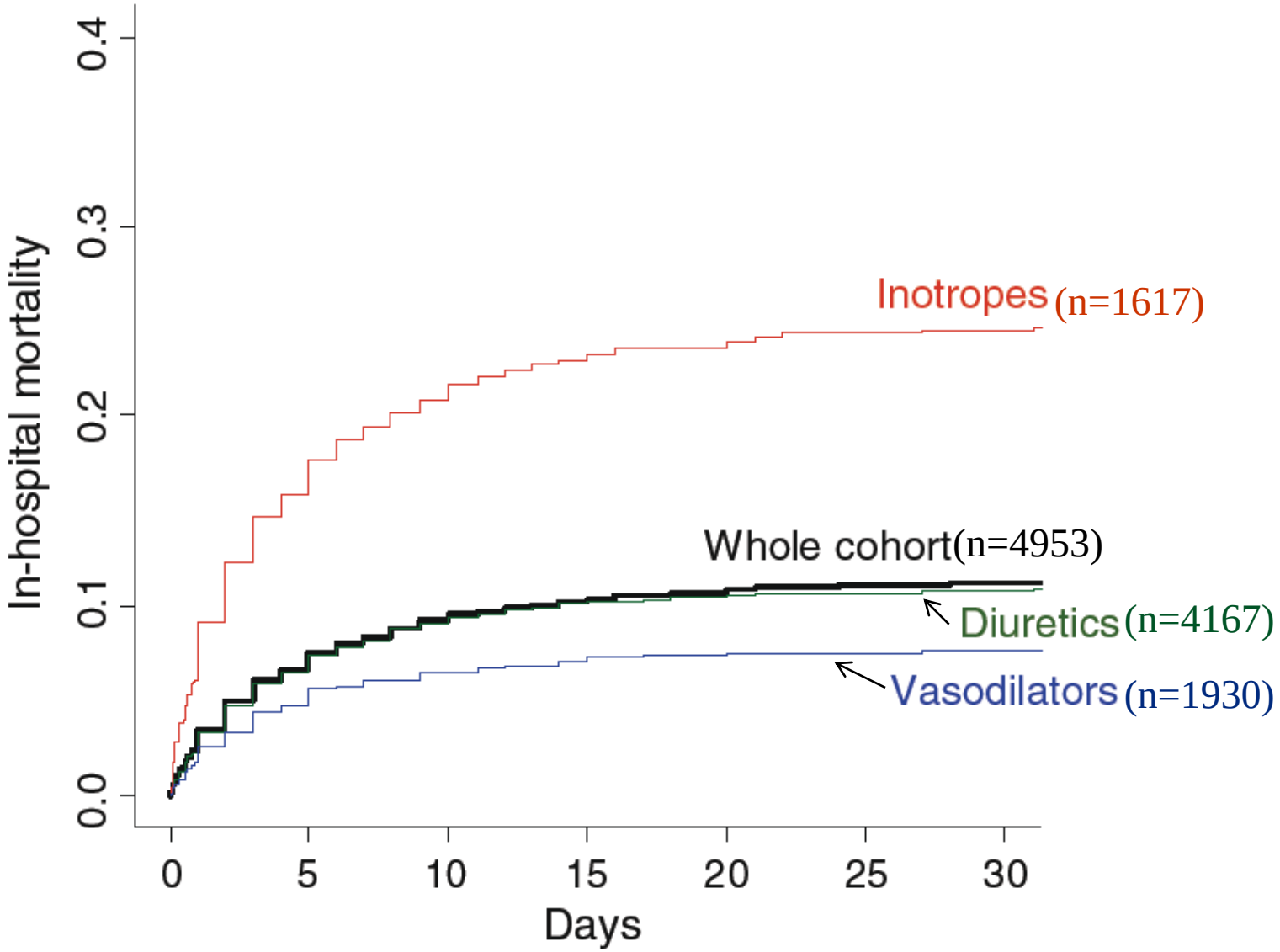


Inotropic Therapies

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

Hasenfuss and Teerlink, EHJ 2011

Effect of IV drugs given during the first 48 hours in AHF patients on in-hospital mortality



Consensus on Circulatory Shock and Hemodynamic Monitoring. TF of the ESICM

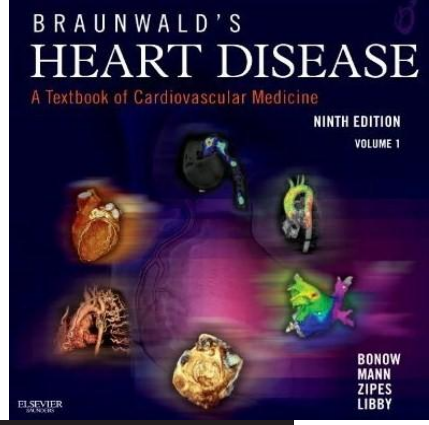
We recommend early treatment, including hemodynamic stabilization and treatment of the shock etiology.

Best practice.

Int Care Med 2014

Diagnosis and Management of Acute Heart Failure

Mihai Gheorghiade, Gerasimos S. Filippatos, and G. Michael Felker



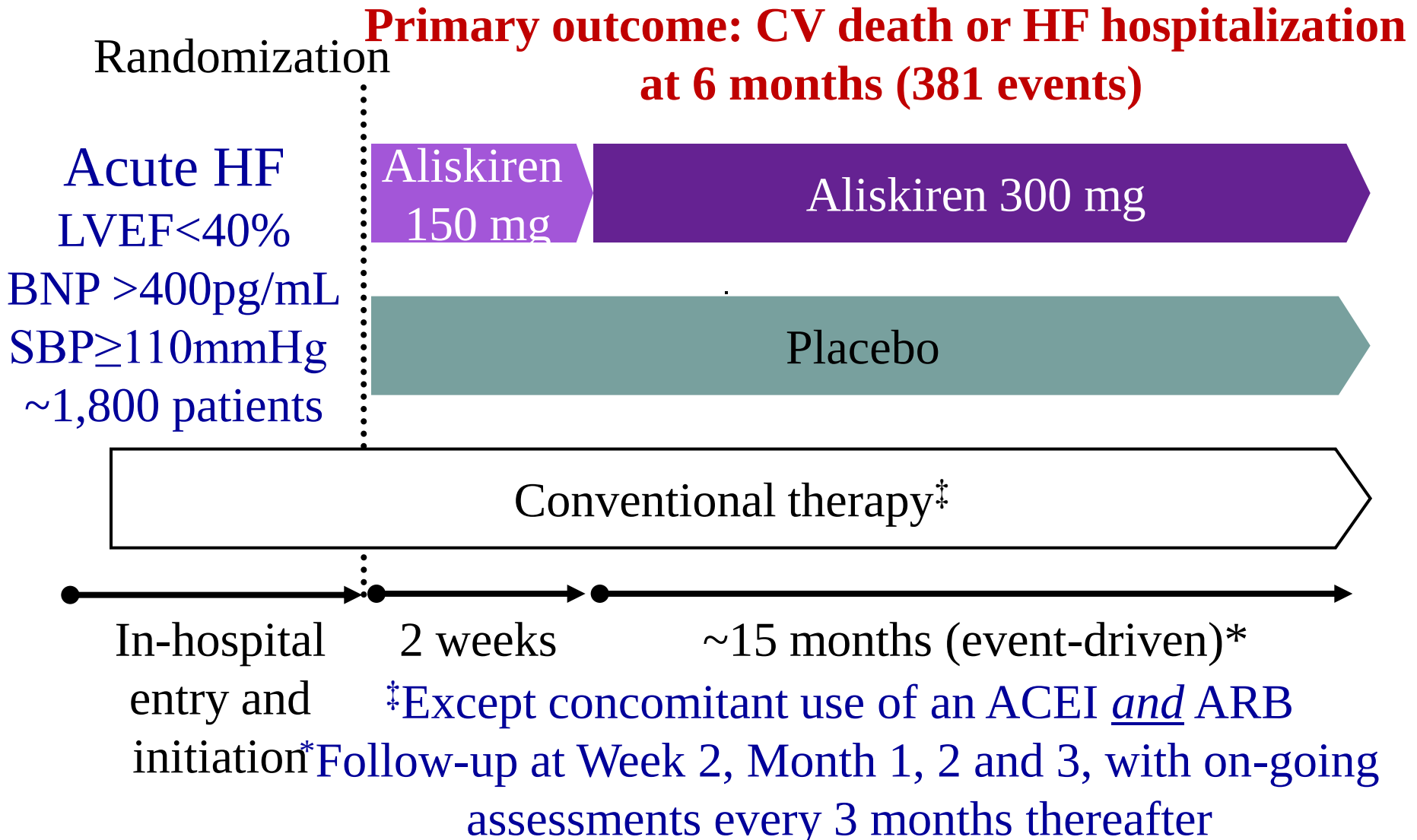
Demographics and Comorbidities of Patients Hospitalized with Acute Heart Failure from Various Registries

	ADHERE N = 105,388	OPTIMIZE-HF N = 48,612	EHFS II N = 3580	ARGENTINA N = 2974
Mean age, years	72	73	70	68
Women, %	52	52	39	41
Prior HF, %	76	88	63	50
Preserved EF, %	40	49	52	26
Medical history, %				
CAD	57	50	54	—
Hypertension	73	71	62	66
Myocardial infarction	31	—	—	22
Atrial fibrillation	31	31	39	27
Diabetes	44	42	33	23
Renal insufficiency	30	20	17	10
COPD/asthma	31	34	19	15

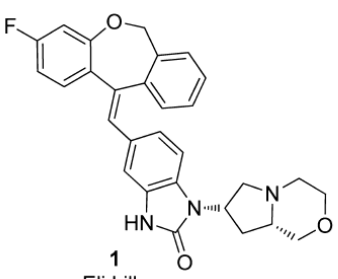
From: Braunwald's Heart Disease. 9th ed. Philadelphia, Elsevier, 2011

ASTRONAUT design overview

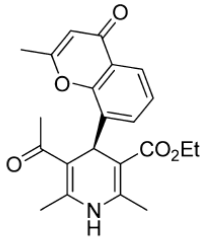
AliSkiren TRial ON Acute heart failure oUTcomes



Non-steroidal MRAs: more selective for cardiac/vascular than renal tissue?



1
Eli Lilly



2
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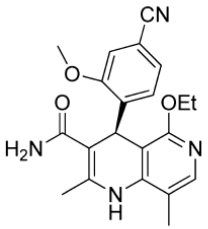
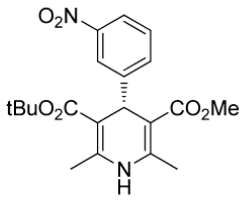
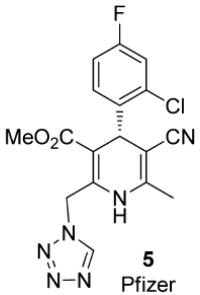


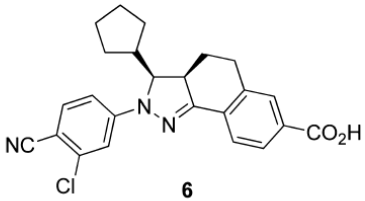
3
Bayer



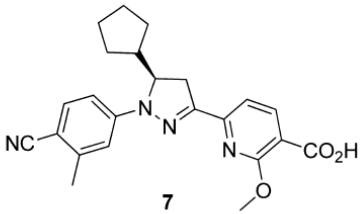
4
(+)-mebudipine



5
Pfizer



6
PF-3882845



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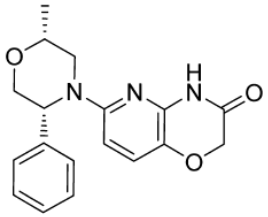

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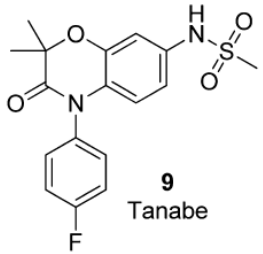

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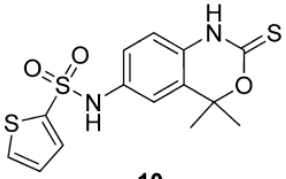

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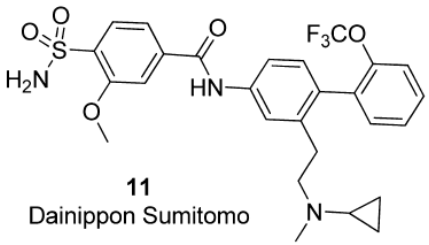

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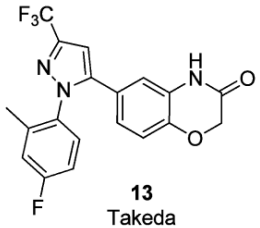

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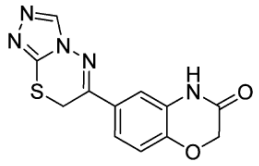

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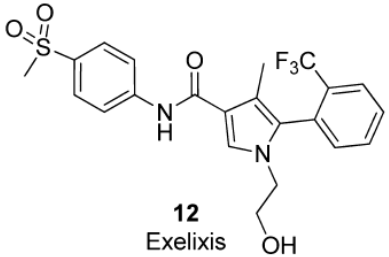

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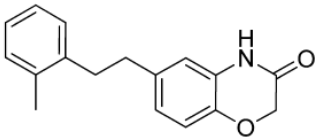

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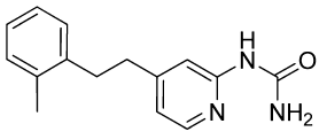

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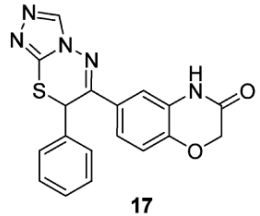

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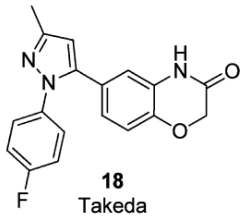

18
Takeda

ARTS

ARTS-HF

Safety and efficacy study of BAY 94-8862 in patients with WCHF and left ventricular systolic dysfunction and either type 2 diabetes mellitus with or without CKD or moderate CKD alone

Primary aim

Investigate efficacy [percentage of patients with a relative decrease in NT-proBNP of more than 30% from baseline to visit 8 (day 90±2)] and safety of BAY 94-8862

Secondary aims

- **Analyse the composite endpoint of death from any cause, cardiovascular hospitalizations, or emergency presentations for WCHF until visit 8 (day 90±2)**
- **Monitor changes in health-related quality of life as assessed by the KCCQ and EQ-5D-3L**

ARTS-DN

Safety and efficacy study of BAY 94-8862 in patients with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

Primary aim

Investigate change in UACR after treatment with BAY 94-8862 once daily over 90 days versus placebo

Secondary aims

- Investigate the safety and tolerability by assessing effects of different doses of BAY 94-8862 on serum potassium and renal function
- Analyse changes in health-related quality of life as assessed by the KDQOL-SF and EQ-5D-3L

- **CoChairs: B. Pitt & G Filippatos**

Conclusions

- The therapeutic approach to acute HF has not changed much in the last few decades
- There is a need to identify treatment strategies and regimens that reduce mortality and the incidence of rehospitalization in AHF patients

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“only dead fish swim with the stream”

japanese proverb