ΟΞΕΙΑ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ
ΘΕΡΑΠΕΥΤΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ

Ιπποκράτειες Ημέρες Καρδιολογίας
27-28 Μαρτίου 2015

Μαρία Παπαδημητρίου
Επιμελήτρια Β΄ Καρδιολογίας
Γενικό Νοσοκομείο Κιλκίς
Οξεία καρδιακή ανεπάρκεια;

Acute Heart Failure

- Acute Heart Failure Syndromes
- Hospitalization for Heart Failure

- Acute Decompensated Heart Failure
- Worsening of Chronic Heart Failure
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation
AHF is the term used to describe the rapid onset of, or change in, symptoms and signs of HF.

It is a life-threatening condition that requires immediate medical attention and usually leads to urgent admission to hospital.
Economic impact

60.6% hospitalization $23.1 billion

38.6% Outpatient care $14.7 billion

0.7% Transplants $270 million

Total $38.1 billion 5.4% of total health care costs
Hospitalization

Rates of readmission
- 2% within 2 days
- 20% within 1 month
- 50% within 6 months

Initial episode
21%

Repeat visit
79%
Κλινική ταξινόμηση
2005 Classification of AHF

- Right HF
- Cardiogenic shock
- PULMONARY EDEMA
- Hypertensive HF
- Acute decompensated congestive HF
- High output failure
- Cardiogenic shock
ESC-HF Pilot Survey\textsuperscript{[1]}: In-Patient Clinical Profiles (available for 1763 patients [93%])

- Cardiogenic shock: 2.3%
- Pulmonary edema: 13.3%
- Hypertension: 4.7%
- Right ventricular HF: 4.7%
- Decompensated HF: 75.0%
In-hospital Mortality

Rudiger[^7] 2005: 8%
Prognostic Factors

- Shock vs no shock
- LVEF
- Renal function
- Age
- Ischemic vs nonischemic
- Serum Na$^+$
- BNP
ESC-HF Pilot Survey\textsuperscript{[1]}: AHF In-hospital All-cause Mortality by Clinical Profile at Entry

AHF in-hospital mortality (3.8% of total patients)

ACUTE HEART FAILURE

High blood pressure
Lung-related factors
Pulmonary embolism
Lung disease
Pulmonary hypertension

Heart-related factors
Valve dysfunction
Rhythm disorders
Heart muscle dysfunction (cardiomyopathy)
Other cardiac disorders (cardiac tamponade)
Myocardial ischaemia

Treatment and lifestyle factors
Excessive salt/fluid intake
Excessive physical activity
Starting certain medication that affect cardiac function or salt retention
Failure to take heart failure medications

Other medical conditions
Anaemia
Renal dysfunction
Thyroid disorders
Diabetes

Infections

Alcohol or drug abuse
BufferData
Diagnosis and treatment in parallel

Suspected acute heart failure

- History/examination (including blood pressure and respiratory rate)
- Chest X-ray
- Echocardiogram or NP (or both)
- Blood chemistry
- ECG
- Oxygen saturation
- Full blood count

Simultaneously assess for

- Ventilation/systemic oxygenation inadequate
- Life-threatening arrhythmia/bradycardia
- Blood pressure <85 mmHg or shock
- Acute coronary syndrome
- Acute mechanical cause/severe valvular disease

Urgent action if present

- Oxygen
- NIV
- ETT and invasive ventilation
- Electrical cardioversion
- Pacing
- Inotrope/vasopressor
- Mechanical circulatory support (e.g., ABP)
- Coronary reperfusion
- Antithrombotic therapy
- Echocardiography
- Surgical/percutaneous intervention

European Heart Journal (2012) 33, 1787–1847
Algorithm for management of acute pulmonary oedema/congestion

Αντιμετώπιση οξείας καρδιακής ανεπάρκειας

- Οξυγόνο
- Διουρητικά
- Μορφίνη
- Αγγειοδιασταλτικά
- Νεσιριτίδη
- Ινότροπα
- Αγγειοσυσπαστικά

- Μη επεμβατικός αερισμός
- Μηχανική υποστήριξη της κυκλοφορίας
- Υπερδιήθηση

European Heart Journal (2012) 33, 1787–1847
**Recommendations**

**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.  

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**High-flow oxygen** is recommended in patients with a capillary oxygen saturation <90% or PaO2 <60 mmHg (8.0 kPa) to correct hypoxaemia.  

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**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.  

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**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).  

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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.  

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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.  

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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.  

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ADHF: therapeutic options

Fluid volume (preload)
- Furosemide
- Bumetanide
- Torsemide

Preload and afterload
- Nitroglycerin
- Nitroprusside
- Nesiritide

Vasodilators and Natriuretic Peptide

Inotropes
- Dobutamine
- Milrinone
- Levosimendan

contractility

contractility
ADHF: therapeutic options

Continue PO Outpt Treatment (GDMT)

Inotropes +/- IV Fluids

Diuretics
Vasodilators

Diuretics
Inotropes

Low Perfusion at Rest?

NO
>2.2L/min/m²
<2.2L/min/m²

YES

Congestion at Rest?

NO
<18
>18

YES

Warm and Dry
Cold and Dry

Warm and Wet
Cold and Wet
Diuretics

• Primarily used to reduce congestion

• Limited literature supporting impact on outcomes

• Diuretic resistance frequently limits efficacy

• Association with increased mortality
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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

• To evaluate the safety and efficacy of various initial strategies of furosemide therapy in patients with ADHF

Route of administration:
  • Q12 hours bolus
  • Continuous infusion

Dosing
  • Low intensification (1 x oral dose)
  • High intensification (2.5 x oral dose)

Acute Heart Failure (1 symptom AND 1 sign) <24 hours after admission

2x2 factorial randomization

- Low Dose (1 x oral) Q12 IV bolus
- Low Dose (1 x oral) Continuous infusion
- High Dose (2.5 x oral) Q12 IV bolus
- High Dose (2.5 x oral) Continuous infusion

48 hours

1) Change to oral diuretics
2) continue current strategy
3) 50% increase in dose

72 hours

Co-primary endpoints

60 days

Clinical endpoints
Conclusions

- There was no statistically significant difference in global symptom relief or change in renal function at 72 hours for either:
  - Q12 bolus vs Continuous infusion
  - Low intensification vs High intensification

Conclusions (2)

• There was no evidence of benefit for continuous infusion compared to Q12 hour bolus on any secondary endpoint.

• Despite transient changes in renal function, there was no evidence for higher risk of clinical events at 60 days associated with the high intensification strategy.

• High intensification (2.5 x oral dose) was associated with trends towards greater improvement in multiple domains:
  • Symptom relief (global assessment and dyspnea)
  • Weight loss and net volume loss
  • Proportion free from signs of congestion
  • Reduction in NT-proBNP.

Diuretics

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. Urine output and signs and symptoms of congestion should be serially assessed, and the diuretic dose should be adjusted accordingly to relieve symptoms, reduce volume excess, and avoid hypotension.

When diuresis is inadequate to relieve symptoms, it is reasonable to intensify the diuretic regimen using either:

a. higher doses of intravenous loop diuretics.

b. addition of a second (e.g., thiazide) diuretic.

Low-dose dopamine infusion may be considered in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow.
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.

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.

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.
Nesiritide

Nesiritide is a human recombinant form of B-type natriuretic peptide

- In 2001, nesiritide was approved by the FDA to reduce PCWP and improve dyspnea

- However, in 2005 two meta-analyses raised concerns regarding the risks of mortality and renal injury.
Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

Maria Rosa Costanzo, MD, FACC,* Maya E. Guglin, MD, FACC,† Mitchell T. Saltzberg, MD, FACC,* Mariell L. Jessup, MD, FACC,‡ Bradley A. Bart, MD, FACC,§ John R. Teerlink, MD, FACC,|| Brian E. Jaski, MD, FACC,¶ James C. Fang, MD, FACC,# Erika D. Feller, MD, FACC,** Garrie J. Haas, MD, FACC,†† Allen S. Anderson, MD, FACC,‡‡ Michael P. Schollmeyer, DVM,§§ Paul A. Sobotka, MD, FACC,§§ for the UNLOAD Trial Investigators
Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio
UNLOAD trial
Ultrafiltration versus i.v. Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

Design: Prospective, randomized trial in patients with ADHF due to volume overload

Population: n=200, ≥ 2 signs of volume overload, randomized within 24 hours of admission, hemodynamically stable, and no prior i.v. vasoactive drugs

Treatment: Ultrafiltration vs. aggressive i.v. diuretic therapy

Endpoints: Weight loss and dyspnea score at 48 hours

Costanzo et al. JACC Vol. 49, No. 6, 2007:675–83
Conclusions

• Early ultrafiltration produces greater weight and fluid loss than IV diuretics, without adverse impact on renal function

• An early ultrafiltration strategy reduces 90 day:
  • Percentage of patients requiring re-hospitalization for HF
  • Number of HF re-hospitalizations
  • Days of re-hospitalization for HF
  • ED and unscheduled office visits

Costanzo et al. JACC Vol. 49, No. 6, 2007:675–83
Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight.

Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy.
Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

Alasdair Gray, M.D., Steve Goodacre, Ph.D., David E. Newby, M.D., Moyra Masson, M.Sc., Fiona Sampson, M.Sc., and Jon Nicholl, M.Sc., for the 3CPO Trialists*
3 CPO trial
Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

Design: Multicentre randomised controlled trial in patients with acute cardiogenic pulmonary edema

Population: n= 1156,
Acute dyspnoea and bilateral crackles on chest auscultation
Chest radiograph confirming the diagnosis
Arterial blood gas analysis with a pH of <7.35
Respiratory rate of >20 breaths per minute

Treatment: Randomised (1:1:1) to:
- Standard oxygen therapy
- CPAP
- NIPPV

Hypothesis: Non-invasive ventilation reduces mortality
Conclusions

In patients with acute cardiogenic pulmonary oedema, non-invasive ventilation:

• Produces more rapid resolution of metabolic abnormalities and respiratory distress

• Has no major effect on 7-day or 30-day mortality

• Is beneficial irrespective of the mode (CPAP or NIPPV) of delivery

Ινότροπα

Evidence for Low Perfusion
- Narrow Pulse Pressure
- Pulsus Alternans
- Cool Forearms and Legs
- May Be Sleepy, Obtunded
- ACE Inhibitor-Related
- Symptomatic Hypotension
- Declining Serum Sodium Level
- Worsening Renal Function

Low Perfusion at Rest?
- NO
  - <2.2L/min/m²
    - NO: Warm and Dry
  - >2.2L/min/m²
    - NO: Warm and Wet
- YES
  - <2.2L/min/m²
    - YES: Cold and Dry
  - >2.2L/min/m²
    - YES: Cold and Wet

Congestion at Rest?
- NO: PCWP: <18
- YES: PCWP: >18

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Інотропа

- **Traditional Inotropes**: dobutamine, milrinone or dopamine

- **New Inotropes** (not approved by FDA)
  - Levosimendan: calcium sensitizer
  - Omecamtiv Mecarbil: cardiac myosin activator
  - Istaroxime: Na/K-ATPase inhibitor

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<th>CO</th>
<th>PCWP</th>
<th>SVR</th>
<th>MAP</th>
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<tr>
<td>Dobutamine</td>
<td>↑↑↑</td>
<td>↓/↔</td>
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<td>Dopamine- moderate</td>
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<td>Milrinone</td>
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<td>Levosimendan</td>
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## Preferred inotrope in different clinical settings

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Agent</th>
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<tr>
<td>Increased PAP</td>
<td>Levosimendan</td>
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<tr>
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<td>Milrinone</td>
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<tr>
<td>Need for beta-blocker</td>
<td>Levosimendan</td>
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<td></td>
<td>Milrinone</td>
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<tr>
<td>Hypotension</td>
<td>Dobutamine</td>
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<td></td>
<td>Dopamine</td>
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<td></td>
<td>Norepinephrine</td>
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<tr>
<td>Worsening renal function</td>
<td>Dobutamine</td>
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<td></td>
<td>Levosimendan</td>
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<tr>
<td>Ischemic disease</td>
<td>Levosimendan</td>
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<td></td>
<td>Dobutamine</td>
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1. Patient heterogeneity
   - Substrate (ischemic/nonischemic, hypertension)
   - Trigger (acute coronary syndrome, arrhythmia...)
   - Pathophysiology (diastolic vs systolic HF)
   - Lack of stratification (SBP...)

2. Absence of reference standard treatment

3. Lack of consensus on endpoints and timing
What Is the Cause of This Mortality Excess?

- **AHF**
  - Congestion
    - Dyspnea
    - Worsening HF
  - End organ failure
    - Myocardial damage
    - Worsening renal function
    - Liver dysfunction

Death
Renal dysfunction is common in patients with heart failure and is associated with high morbidity and mortality. Cardiac and renal dysfunction may worsen each other through multiple mechanisms such as fluid overload and increased venous pressure, hypo-perfusion, neurohormonal and inflammatory activation, and concomitant treatment. The interaction between cardiac and renal dysfunction may be critical for disease progression and prognosis. Renal dysfunction is conventionally defined by a reduced glomerular filtration rate, calculated from serum creatinine levels. This definition has limitations as serum creatinine is dependent on age, gender, muscle mass, volume status, and renal haemodynamics. Changes in serum creatinine related to treatment with diuretics or angiotensin-converting enzyme inhibitors are not necessarily associated with worse outcomes. New biomarkers might be of additional value to detect an early deterioration in renal function and to improve the prognostic assessment, but they need further validation. Thus, the evaluation of renal function in patients with heart failure is important as it may reflect their haemodynamic status and provide a better prognostic assessment. The prevention of renal dysfunction with new therapies might also improve outcomes although strong evidence is still lacking.
Cardio-renal interactions in heart failure and kidney disease

The cardio-renal syndrome

- Decreased cardiac performance
- Neurohormonal activation, inflammation, oxidative stress, anemia
- ↑ NaH₂O retention/diuretic resistance
- ↓ Renal perfusion, ↑ Renal venous pressure
- Renal function adenosine release others?

Type of mechanism: Haemodynamic
Neuroendocrine, humoral, local (renal)

Metra M et al. Eur Heart J 2012;33,2135-2143
CONCLUSION AND RELEVANCE  In participants with acute heart failure and renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.
Relaxin

- Peptide hormone
- Similar in size and shape to insulin (MW 5963)
- Found in men and women
- Normal hormone of pregnancy
- Women “exposed” for 9 months to increased plasma concentrations: 0.8-1.6 ng/ml pregnancy*

Szlachter et al, *Obstet & Gynecol* 1982;59:167-70
Relaxin: Mechanisms of Action

- Vasodilation
  - NO, cGMP effectors
  - Induction of NOS II/III
  - Upregulation of ETB receptor
- Preferential dilation of constricted vessels
- Anti-inflammatory
- Anti-apoptotic
- Anti-fibrotic

Teichman, SL, et al. *Heart Fail Rev* 2009
The RELAX-AHF Program

Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study

John R Teerlink, Marco Metra, G Michael Felker, Piotr Ponikowski, Adriaan A Voors, Beth Davison Weatherley, Alan Marmor, Amos Katz, Jacky Grzybowski, Elaine Umemori, Sam L Teichman, Gad Cotter

Summary
Background Most patients admitted for acute heart failure have normal or increase blood pressure. Relaxin is a natural human peptide that affects multiple vascular control pathways, suggesting potential mechanisms of benefit for such patients. We assessed the dose response of relaxin's effect on symptom relief, other clinical outcomes, and safety.

Methods In a placebo-controlled, parallel-group, dose-ranging study, 234 patients with acute heart failure, dyspnoea.

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 Umemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alan Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angela Trapani, Christoph A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAX in Acute Heart Failure (RELAX-AHF) Investigators

Summary
Background Serelaxin, recombinant human relaxin-2, is a vasoactive peptide hormone with many biological and haemodynamic effects. In a pilot study, serelaxin was safe and well tolerated with positive clinical outcome signals in patients with acute heart failure. The RELAX-AHF trial tested the hypothesis that serelaxin-treated patients would have greater dyspnoea relief compared with patients treated with standard care and placebo.
How can we reduce mortality?

- Myocardial injury (troponin release)
- Renal dysfunction (cardiorenal syndrome)
- Liver dysfunction

PREVENTION OF END-ORGAN DAMAGE

Mortality

Congestion

Viable but dysfunctional myocardium

Neurohormonal and inflammatory activation

Mechanisms that can be targeted

- Hemodynamic deterioration (↑ LVFP, ↓ CO, ↓ perfusion)
- Vascular resistance/↑ stiffness

Metabolic factors
Ευχαριστώ πολύ για την προσοχή σας!