‘Time to therapy ’ concept in AHF Syndromes – Treat early or die?

M. Birhan Yılmaz M.D, FESC
Professor of Medicine
Department of Cardiology
Cumhuriyet University
Sivas, TURKEY
• Time to therapy concept in CV disease
• Time concept in AHF: Overlooked data so far
• Recent data and paradigm shift

Disclosures: PI in Novartis and Cardiorentis studies
Time Dependency: Understanding the Concept

Treat Early or Die

VENTRICULAR TACHYCARDIA
ACUTE MYOCARDIAL INFARCTION
CEREBROVASCULAR ACCIDENT
PNEUMONIA
HYPOGLYCEMIA
HYPOXIA

TIME IS IMPORTANT
Think outside the box

• Where AHF stands with regard to time?
• Any evidence???:

Data derived from prospective randomized study versus registry

What am I supposed to measure?: «Dyspnea» and/or «outcome»
Question: Is there an opportunity window for AHF just like other diseases?
Answer: Probably yes...
Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)

Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods
ALARM-HF: IV treatment at admission
Results from ALARM

- IV diuretics and IV vasodilators were started at a median of 0.5 \([0.0 – 1.0]\) hour and 0.5 \([0.0 – 2]\) hour respectively after admission.
- IV vasodilators were quasi-exclusively nitrates: nitroglycerine in 76 % and isosorbite dinitrate 19 %
- In-hospital mortality:
  - Before matching 7.6 vs 14.2 % with and without vasoD
  - After matching 7.8 versus 11 % with and without vasoD
Early Vasoactive Drugs Improve HF Outcomes

- ADHERE Registry: N=35,700
  - examined the relationship between vasoactive time and inpatient mortality within 48 hours of hospitalization.

- Early vasoactives defined as <6 hours
  - Early: 22,788 (63.8%)  Late: 12,912 (36.2%)

- Median vasoactive time:
  - Early 1.7 hours  Late 14.7 hours

- In-hospital mortality was lower in the early therapy group
  - (OR 0.87; 95% CI 0.79–0.96; P=.006)

- The adjusted odds of death increased 6.8% for every 6 hours of treatment delay (95% CI 4.2–9.6; P<.0001)

Time to therapy versus mortality

288 hospitals
163,457 ADHF hospitalizations
46,811 (29%) received vasoactives

Mortality vs. Quartiles of Diuretic Time & BNP Level

Maisel AS, Peacock WF. JACC 2008; 52(7) 534-540
Study design and drug procedures

Nesiritide

Acute HF < 24 hrs from IV RX

24–168 hrs Rx

Placebo

Co-primary endpoint:
Dyspnea relief at 6 and 24 hrs

Co-primary endpoint:
30-day death or HF rehosp

All-cause mortality at 180 days

- 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 per investigator based on clinical improvement
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization (n=6836)

- **Hazard Ratio 0.93 (95% CI: 0.8, 1.08)**

  - Placebo: 10.1%
  - Nesiritide: 9.4%

  **P=0.31**

Risk Diff (95% CI):
- 30-day Death/HF Rehospitalization: -0.7 (-2.1; 0.7)
- 30-day Death: -0.4 (-1.3; 0.5)
- HF Rehospitalization: -0.1 (-1.2; 1.0)

O’Connor et al NEJM 2011
Overall effect of time from presentation to study drug on 6 hour dyspnea relief

P = <0.001

Relative Odds for Better Status Dyspnea (Higher is Better)

Time to Drug (hours)

0 to 4: 838
4 to 8: 1353
8 to 16: 659
16 to 20: 538
20 to 24: 882
24 to 28: 1341
28 to 32: 883
32 to 36: 239
>36: 274
<table>
<thead>
<tr>
<th>Subject Category</th>
<th>6 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>N=6860</td>
<td>N=6769</td>
</tr>
<tr>
<td>Inotropes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>N=6574</td>
<td>N=6481</td>
</tr>
<tr>
<td>Yes</td>
<td>N=286</td>
<td>N=288</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>N=5912</td>
<td>N=5835</td>
</tr>
<tr>
<td>Any IV Vaso</td>
<td>N=943</td>
<td>N=929</td>
</tr>
<tr>
<td>No IV Nitro</td>
<td>N=5965</td>
<td>N=5886</td>
</tr>
<tr>
<td>IV Nitro</td>
<td>N=894</td>
<td>N=882</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>N=691</td>
<td>N=679</td>
</tr>
<tr>
<td>Yes</td>
<td>N=6169</td>
<td>N=6090</td>
</tr>
<tr>
<td>Study Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>N=2612</td>
<td>N=2564</td>
</tr>
<tr>
<td>Yes</td>
<td>N=4248</td>
<td>N=4205</td>
</tr>
<tr>
<td>Time from Hosp to Rand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15.5</td>
<td>N=3428</td>
<td>N=3369</td>
</tr>
<tr>
<td>≥15.5</td>
<td>N=3432</td>
<td>N=3400</td>
</tr>
</tbody>
</table>

**Dyspnea at 6 and 24 Hours**

**Odds for Marked-Moderate Improvement**

OR <1: Favors Placebo; OR >1: Favors Nesiritide; Odds Ratio of Markedly/Moderately vs. Other
Estimate of effect of nesiritide on 6 hour dyspnea relief based on time from presentation to study drug

Chi-square for treatment = 9.66 for 2 d.o.f., p = 0.0080
Think outside the box

- Treat at admission: Time to therapy (TtT concept)
  - Including patients >12-24 hours of admission was wrong!
Effects of prehospital medications on mortality and length of stay in congestive heart failure.

Wuerz RC, Meador SA

Division of Emergency Medicine, Milton S Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey.

Abstract

HYPOTHESIS: Prehospital medications for congestive heart failure should affect hospital outcomes (survival and length of stay).

STUDY DESIGN: In a retrospective case series, hospital outcomes were compared for patients treated with prehospital nitroglycerin, furosemide, and/or morphine (252) versus those given no medications (241).

SETTING: A rural/suburban emergency medical services system (population 140,000) served by three paramedic units.

PARTICIPANTS: Four hundred ninety-three consecutive cases of congestive heart failure or pulmonary edema were identified by hospital discharge diagnosis from a data base of 8,315 paramedic transports with known outcome.

INTERVENTIONS: Oxygen was given by protocol to 489 patients. Other medications were given by order of on-line physician medical command.

RESULTS: Overall mortality was 10.9% (54 of 493). Treated and untreated patients were comparable in age, sex, cardiac rhythms, prior use of cardiac medications, and response and scene times; mortality was reduced in treated versus untreated patients (odds ratio for improved survival, 2.51; 95% confidence interval, 1.37 to 4.55; P less than .01). Positive treatment effect was greatest for 58 nonhypotensive, critical patients (odds ratio for survival, 10.25; P less than .01). No single drug combination was unique in terms of treatment benefit. Patients treated in the field received medications 36 minutes earlier than patients first treated in the emergency department. No survival benefit was evidence for noncritical, nonhypotensive patients, and patients with final diagnoses of asthma, chronic obstructive pulmonary disease, pneumonia, or bronchitis had a higher than expected mortality if erroneously treated for congestive heart failure. Differences in hospital length of stay were not significant for any group.

CONCLUSION: Prehospital medications improve survival in congestive heart failure, especially in critical patients. More than one combination of medications seems effective, and early treatment is associated with improved survival. However, these medications appear to increase mortality in patients misdiagnosed in the field. Factors used in paramedica and medical command assessments require further study.

If treated,
OR of survival 2.51 (1.37-4.55) p<0.01
Early CPAP vs Late CPAP

**Early CPAP group**
- **T0**: HOME
  - n = 63
- **T15′**: CPAP 7.5 cmH₂O
  - n = 62
- **T30′**: CPAP 7.5 cmH₂O + Medical treatment
  - n = 62
- **T45′**: Medical treatment alone

**Late CPAP group**
- **T0**: AMBULANCE
  - n = 61
- **T15′**: CPAP 7.5 cmH₂O + Medical treatment
  - n = 53
- **T30′**: Medical treatment alone
  - n = 53
- **T45′**: Medical treatment alone

Early CPAP vs Late CPAP

(A) PaCO₂ (mmHg)

(B) PaO₂ (mmHg)

* p < 0.05

## Early CPAP vs Late CPAP

<table>
<thead>
<tr>
<th></th>
<th>Early CPAP</th>
<th>Late CPAP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation Rate</td>
<td>6</td>
<td>16</td>
<td>0.01</td>
</tr>
<tr>
<td>Intubation between T0 and T15</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Need for Dobutamine</td>
<td>0</td>
<td>5</td>
<td>0.02</td>
</tr>
<tr>
<td>In-hospital Mortality</td>
<td>2</td>
<td>8</td>
<td>0.05</td>
</tr>
</tbody>
</table>

The earlier, the better


Department of Anesthesiology and Critical Care Medicine, INSERM U942, University Paris Diderot, Paris, France.

Dyspnoea at 6 Hours from Baseline by 7-point Likert in AHFS

Mebazaa et al. Eur Heart J 2010;31(7):832-41
• Dyspnea is present in most patients at admission for AHF
• Orthopnea could help differentiating AHF from non-AHF
• Most of the patients have dyspnea that is improved within 6 hours
• VAS is an excellent tool to measure dyspnea
• IF dyspnea and «improvement in dyspnea» are the «optimal» or «must» inclusion criteria for trials

• Concerning clinical trials:
  • Who are the patients that are included in the trials and are still dyspneic after 24-48 hours?
  • If dyspnea is so rapidly improved by conventional treatment, is there any room for «new» agents?
Any recent data?
Serelaxin, Recombinant Human Relaxin-2, For Treatment of Acute Heart Failure (RELAX-AHF): A Randomized, 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

RELAX-AHF Methods

- International, double-blind, placebo-controlled trial

**Patients**

- Admitted to hospital for acute heart failure
- Randomly assigned to standard care plus 48-h intravenous infusions of placebo or serelaxin (30 μg/kg per day) **within 16 h from presentation.**
- Dyspnea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP, mild-to-moderate renal insufficiency, and systolic blood pressure greater than 125 mmHg.
<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=580)</th>
<th>Serelaxin (n=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.5 (10.8)</td>
<td>71.6 (11.7)</td>
</tr>
<tr>
<td>Men</td>
<td>357 (62%)</td>
<td>368 (63%)</td>
</tr>
<tr>
<td>White</td>
<td>552 (95%)</td>
<td>544 (94%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.8 (18.7)</td>
<td>81.9 (18.5)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>29.5 (6.1)</td>
<td>29.1 (5.3)</td>
</tr>
<tr>
<td>Region*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>282 (49%)</td>
<td>280 (48%)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>101 (17%)</td>
<td>103 (18%)</td>
</tr>
<tr>
<td>USA</td>
<td>55 (9%)</td>
<td>59 (10%)</td>
</tr>
<tr>
<td>Argentina</td>
<td>37 (6%)</td>
<td>34 (6%)</td>
</tr>
<tr>
<td>Israel</td>
<td>105 (18%)</td>
<td>105 (18%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>142.1 (17.0)</td>
<td>142.2 (16.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81.7 (13.2)</td>
<td>82.2 (14.2)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>80.4 (14.9)</td>
<td>78.9 (15.0)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td>22.0 (4.6)</td>
<td>21.8 (4.6)</td>
</tr>
<tr>
<td>Time from presentation to randomisation (h)</td>
<td>7.9 (4.7)</td>
<td>7.8 (4.6)</td>
</tr>
<tr>
<td>Intravenous nitrates at randomisation</td>
<td>42 (7%)</td>
<td>39 (7%)</td>
</tr>
</tbody>
</table>

No significant effects were recorded for the secondary endpoints of cardiovascular death or readmission to hospital for heart failure or renal failure.
A  
Placebo: 55 cardiovascular deaths (9.6%)  
Serelaxin: 35 cardiovascular deaths (6.1%)  
HR 0.63 (95% CI 0.41-0.96)  
p=0.028  
n=580

B  
Placebo: 65 deaths (11.3%)  
Serelaxin: 42 deaths (7.3%)  
HR 0.63 (95% CI 0.43-0.93)  
p=0.02  
n=580

Number at risk  
Placebo 580 567 559 547 535 523 514 444 580 567 559 547 535 523 514 444  
Serelaxin 581 573 563 555 546 542 536 463 581 573 563 555 546 542 536 463
In RELAX-AHF, a 48-h infusion of serelaxin resulted in mild improvements in measures of dyspnoea, associated with significant reductions in early worsening heart failure events, signs and symptoms of congestion, initial length of hospital stay, and duration of intensive care.

However, there was no improvement in readmission to hospital for heart failure or renal failure.

A 37% reduction in cardiovascular and all-cause mortality was also noted in the serelaxin-treated patients.

Serelaxin mildly reduced blood pressure, and was well tolerated with no notable difference in the overall adverse event profile and a lower rate of renal adverse events compared with placebo.
Clevidipine Improves Dyspnea in ED Acute Heart Failure: A Randomized, Open Label Study

Peacock WF, Baylor College of Medicine, Houston, TX
Chandra A, Kaiser Permanente, Sacramento, CA
Collins S, Vanderbilt University, Nashville, TN
Fonarow G, University of California LA, Los Angeles, CA
Garrison N, Drug Research & Analysis, Montgomery, AL
Mebazaa A, University Paris, Paris, France
Enrollment

- Physicians generally specified target BP 15%-30% lower than the presentation SBP
- Most patients (86.8%) in the SOC group received
  - Nitroglycerin (56.6%)
  - Nicardipine (30.2%)
- 13.2% in the SOC group received
  - IV ISDN (4), hydralazine (1), diltiazem (1), SNP (1)

Median (IQR) Time To Treatment
(ER door to randomization)
- CLV 2.8 hrs (2.2, 3.8)
- SOC 2.6 hrs (1.8, 3.6)
Early BP Reduction

- Mean Change from Baseline in SBP (mITT)
**SECONDARY ENDPOINT**

VAS score over time (Confirmed AHF)

- \( \Delta = -10.4 \text{ mm, } p = 0.017 \)
- \( \Delta = -11.7 \text{ mm, } p = 0.020 \)
- \( \Delta = -14.0 \text{ mm, } p = 0.015 \)

\( p = 0.037 \) for treatment x time effect
Is there a golden hour?

- Probably yes....
All AHF patients should receive appropriate goal directed therapy as soon as possible, regardless of their location.

- In hypertensive HF patients with significant dyspnoea, treatment with vasodilator therapy should not be delayed pending diagnostic testing.