Highlights of the Congress

Drug therapy

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Disclosures

• **Grants, trials, advisory boards, honoraria**
  • Gilead, Berlin-Chemie/Menarini, Novartis, Astra-Zeneca, Novartis, Sanofi, Servier, Daiichi-Sankyo, Lilly

• **My apologies**
  • to all the authors that unfortunately could not be summarized in this 15 min talk

Aliskiren
Serelaxin
BAY 94-8862
Coenzyme Q10
L-Carnosine
β-blockers
Ivabradine
Mildronat
Trimetazidine
Furosemide
Allopurinol
The effect of Coenzyme Q10 on morbidity and mortality in chronic heart failure

Results from the Q-SYMBIO study

Svend Aage Mortensen, MD, DMSc, FESC
on behalf of the Q-SYMBIO Study Investigators
Q-SYMBIO: background and methods

- **Coenzyme Q10 (CoQ10, ubiquinone)** is an essential factor for energy production (electron transport chain) and a powerful antioxidant and may support the energy starved myocardium in HF.
  - Plasma CoQ10: low level is an independent predictor of mortality in heart failure.
  - Myocardial CoQ10: the level is inversely related to the severity of heart failure.

- **Q-SYMBIO is the first CoQ10 intervention trial powered to address survival in heart failure.**

- **Patients in NYHA Classes III-IV were randomly assigned to either CoQ10 100 mg 3 times daily or placebo on top of conventional therapy.**

- **The primary long-term endpoint was composite MACE using a time to first event analysis.**
  - MACE: hospitalisation for worsening heart failure, cardiovascular death, urgent cardiac transplantation and mechanical support.
  - Secondary long-term endpoints: NYHA Class, NT-proBNP, echocardiography.
Q-SYMBIO: results and conclusions

- 420 patients with similar baseline characteristics were enrolled with a follow-up time of 2 years.

- Primary endpoint was reached by 14% in the CoQ10 group vs. 25% in the placebo group by intention to treat analysis; hazard ratio 2.0 (CI 1.3-3.2), P=0.003.
  - CoQ10 group had significant improvement of NYHA Class (P=0.047) and fewer adverse events than the placebo group.
  - CoQ10 group had lower CV mortality: 8% vs. 15% (P=0.02), lower incidence of hospitalisations for HF (P=0.05) and lower all cause mortality: 9% vs. 17% (P=0.01) compared to placebo.

- Q-SYMBIO verifies that CoQ10 treatment is safe and improves symptoms and survival.

- CoQ10 should be considered as adjunctive therapy of patients with chronic heart failure.
ARIANA-CHF-RD trial

A double-blind, placebo-controlled, randomized trial investigating the safety and efficacy of Additive Renin Inhibition with Aliskiren on renal blood flow and Neurohormonal Activation in patients with Chronic Heart Failure and Renal Dysfunction

Nicolas F. Schroten M.D.
University Medical Center Groningen, University of Groningen, The Netherlands
ARIANA-CHF-RD trial

Study Design

• **Study Population**
  - Stable Heart Failure with Reduced Ejection Fraction (LVEF<45%)
  - Impaired kidney function (eGFR-MDRD 30-75 ml/min/m²)

• **Treatment**
  - Aliskiren vs. Placebo 300 mg daily (on top of ACEi/ARB), n=100 (2:1 ratio)

• **Primary Outcome**
  - Change in Renal Blood Flow (measured with radio-active labeled tracers)
ARIANA-CHF-RD trial

Results

Aliskiren:
- Effectively reduced Plasma Renin Activity (PRA)
- Did not significantly impact Renal Blood Flow (RBF)
- Was associated with a decrease in Glomerular Filtration Rate (GFR) and Filtration Fraction (FF)
- Halted prematurely after early termination of the ALTITUDE trial

Schroten
Patients with acute heart failure (n=1615) requiring hospitalization

Study, whether aliskiren (renin inhibitor, 150-300 mg) reduces the rate of CV death or HF re-hospitalization when added to standard therapy within 6 months (primary EP)
- EF≤40%, ↑BNP, sBP≥110 mmHg, GFR ≥ 40 ml/min/1.73m² (mean 67) or K ≤5 mM
- Follow-up 11.3 months
- 41% with diabetes

Diabetes vs. non-diabetes (prespecified)
- Diabetes: No difference in primary endpoint after 12 months (HR 1.16 for aliskiren)
- No diabetes: significant reduction in primary endpoint (HR 0.80 for aliskiren) and all cause mortality (HR 0.69)
ARTS

a randomized, double-blind, phase 2 trial of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease

Faiez Zannad, Nancy, France
Design: part B with BAY 94-8862 (next generation, non-steroidal mineralocorticoid receptor antagonist, MRA)

666 patients screened; 393 patients randomized
Randomization to BAY 94-8862: Placebo: Spironolactone 1:1:1:1:1:1

Screening

Visit 1 (Baseline)  OD, 25 mg

Visit 4 (Day 15 ± 1)  OD, 50 mg

Visit 7 (Day 29 ± 2)  N = 66; OD, BAY 2.5 mg

N = 67; OD, BAY 5 mg

N = 67; OD, BAY 10 mg

N = 65*; BID, BAY 5 mg

N = 65; Placebo

N = 63; Open treatment arm
Spironolactone

*One randomized patient did not receive any study drug and was therefore excluded from subsequent analyses.
BID, *bis in die* (twice daily); OD, once daily

www.escardio.org/HFA
Summary

- Compared with spironolactone (37 mg), BAY 94-8862 at all investigated doses resulted in:
  - Smaller increases in serum potassium and creatinine
  - Fewer hyperkalaemia/worsening renal function adverse events
  - Smaller decrease in systolic blood pressure

- BAY 94-8862 at doses of at least 5 mg/day
  - Increased serum aldosterone (vs placebo), as a consequence of MR blockade
  - Decreased BNP/NT-proBNP (vs placebo) with reductions at least similar to those resulting from 25/50 mg spironolactone once daily

BNP, B-type natriuretic peptide; MR, mineralocorticoid receptor; NT-proBNP, amino-terminal pro-B-type natriuretic peptide
Effects of oral administration of L-Carnosine and exercise training in patients with chronic heart failure and severe left ventricular dysfunction

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Effects of oral administration of L-Carnosine and exercise training in patients with CHF and severe LV dysfunction

**Background:** L-Carnosine is an endogenous dipeptide (beta-alanyl-L-histidine) expressed at in myocardium with anti-oxidant and free radicals scavenger properties.

- Experimental studies showed that L-Carnosine is involved in the regulation of Ca\(^{2+}\) concentrations in cardiac myocytes and increases contractility when perfused into isolated animals hearts

**Purpose:** To analyze the effects of exercise training and oral administration of orodispersible L-Carnosine in pts with CHF and severe LV dysfunction

**Methods:** 30 pts on optimal medical therapy were randomized in 3 groups:

- 10 pts received L-Carnosine (500 mg OD) in addition to an aerobic exercise training protocol. 10 pts received only L-Carnosine, and 10 pts received no drug in a control group.

- Cardiopulmonary stress test, 6 minutes walking test (6MWT), and QoL tests were performed at baseline and after 6 months.
Effects of oral administration of L-Carnosine and exercise training in patients with CHF and severe LV dysfunction

Results

• Pts receiving L-Carnosine and exercise training had an improvement in 6MWT distance (p=0.032) and in QoL measured with EQ-5D test (p=0.003) and VAS (p=0.023)

• Administration of L-Carnosine when associated with aerobic exercise training was associated with an improvement in the variation of peak VO₂ (p<0.001) compared with the L-Carnosine without exercise training.

• Compared with the control group, L-Carnosine added to exercise training program was associated with a significant improvement in the variation of peak VO₂ (p<0.001), VO₂ at anaerobic threshold (p 0.011), maximal work load (p 0.02), 6MWT distance (p=0.029) EQ-5D test (p=0.02) and VAS (p<0.001)

Conclusions

• Oral administrations of L-Carnosine added to conventional therapy had beneficial effects on exercise performance and QoL in CHF.

• The association between oral L-Carnosine and exercise training improved functional capacity more than only administration L-Carnosine.
Effects of High Dose Allopurinol on Clinical Outcome, Cardiac Function, Quality of Life and Effort Capacity in Patients with Symptomatic Chronic Heart Failure

ALLO-HF Study

Assoc. Prof. Adriana Mihaela ILIESIU
“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
Effects of high dose allopurinol on clinical outcome, cardiac function, QoL and effort capacity in patients with symptomatic CHF

• **Background.** Allopurinol (allo) improves oxidative stress, inflammation, cardiac remodeling and function and reduces CHF progression, but usual doses have different effects.

• **Purpose.** Effects of high dose allo (600 mg/day) on cardiac function, QoL, effort capacity and serum uric acid (SUA) in symptomatic CHF.
  
  • **Study group:** 57 pts with CHF, NYHA class III, EF ≤40%, ischemic and non-ischemic cardiomyopathy, creatinine < 2.0 mg/ml, under optimal drug therapy
  
  • **Method:** NYHA class, NTproBNP, ejection fraction (EF) and E/e’ ratio at echocardiography, Minessota score, 6MWT, and SUA levels, were assessed at baseline and after a 6 months of treatment

• **Results.** After 6 months, NYHA class improved in 23 pts (40.3%), was unchanged in 26 pts (45.6%) and worsened in 2 pts, 2 pts died and 4 pts had cutaneous adverse reactions;

• SUA was 7.9 mg/dl and decreased to 4.4 mg/dl, with greater reduction in NYHA class II pts (4.2 vs 5.5mg/dl, p <0.04)
Effects of high dose allopurinol on clinical outcome, cardiac function, QoL and effort capacity in patients with symptomatic CHF

- NTproBNP decreased with greater reduction in NYHA class II pts and there was a correlation between changes in SUA and NTproBNP (r=0.37);

- LVEF and diastolic function (E/e’) significantly improved and the reduction in SUA was significantly greater in NYHA class II pts;

- QoL and effort capacity improved in 2/3 of pts and were associated with greater reduction in SUA:
  - Minnesota score improved in 33 pts (64.7%) and was associated with greater reduction in SUA (5 mg/dl vs 2.4 mg/dl, p=0.02).
  - 6MWT increased in 34 pts (66.6 %) and was associated with greater reduction in SUA (4.6 mg/dl vs 2.4 mg/dl, p=0.01).

- **Conclusion.**
  1. High dose allo has therapeutic effects on CHF clinical outcomes in relation to the magnitude of SUA reduction.
  2. SUA seems to be a valuable biomarker to assess the efficacy of allo treatment in CHF.
Trimetazidine therapy in patients with dilated cardiomyopathy and CHF

Al Bashir hospital
Amman, Jordan

Dr. Natalia Al Shawabkeh, MD, PhD
Study design

• **Purpose:** analyse of trimetazidine (TMZ) therapy in patients with DCMP and CHF. **Methods:**
  • 40 patients (13-51 years) with DCMP (including idiopathic, congenital and postpartum CMP) and CHF were treated with TMZ during 2 years in a prospective study.
  • Patients with IHD were excluded from the study as well as patients with renal failure, hepatic failure, systemic hypertension and diabetes mellitus.

• **The patients were randomised into two groups.**
  • Group A (n=20) who received β-blockers, digoxin, ACE-i/ARBs, diuretics, MRA, and antiplatelets.
  • Group B (n=20) who received the same treatment and oral TMZ in daily dose 60-70 mg divided in 2-3 doses.

• **The following parameters were monitored:**
  • NYHA class,
  • Maximal ST segment depression,
  • LV, left atrium (LA) dimensions, EF,
  • Stage of diastolic LV dysfunction (normal diastolic function, abnormal relaxation, pseudo normal, restrictive physiology).
Results of the study

• **Differences (p<0.05) were observed in:**
  - NYHA class (improved in 65% of patients in group B versus 45% in group A),
  - Maximal ST segment depression (diminished by 0.9 mm in group B versus 0.4 mm in group A),
  - EF (increased by 9.8% in group B versus 4.3% in group A),
  - LA size (decreased by 1.9 mm in group B and by 0.6 mm in group A).

• **There were no significant differences in LV size and stage of diastolic LV dysfunction.**

• **Conclusion:**
  - TMZ improves symptoms and cardiac function in patients with DCMP and CHF.
  - TMZ treatment seems to be an adjunctive therapeutic option in treatment of patients with DCMP and CHF.
  - This approach should be supported by large scale studies and long-term follow up.
Influence of metabolic therapy with Mildronat on left and right ventricular function (tissue doppler study)

N 60897

M. Tsverava. Tbilisi, Georgia
Objective, Material and methods

- The aim was to study the influence of Mildronat left and right ventricular EchCG and Tissue Doppler (TD) parameters in patients with heart failure.

- We studied 18 patients with NYHA II-III class HF due to ischemic cardiomyopathy. At last during 3 months all patients where in stable state and take standard therapy for HF.

- Standard EchCG and Pulsed Wave TD examination was done from basal parts of interventricular septum, lateral wall of the left and right ventricles before beginning and after 2 months of treatment with Mildronat 1000 mg day.
• **After 2 months of treatment with Mildronat:**
  • left ventricular fractional shortening (13.5±2.0% versus 19.9±4.3%; p<0.01) and EF (34.5±8.2% versus 41.2±4.8%; p<0.01) was increased. Pulmonary arterial acceleration time, right ventricular isometric shortening velocity (10.7±3.3cm/sec versus 13.5±3.5 cm/sec; p<0.05) increased and right ventricular isometric relaxation time (100.2±16.5 msec versus 50.3±24 msec; p<0.01)
  • The index E/e IVS significantly decreased (21.91±6.23 versus 16.06±6.67 respectively; p<0.05), which indicates decrease of left ventricular end diastolic pressure.

• **Addition of Mildronat to traditional medical treatment of HF**
  • improves left ventricular systolic function
  • increases the pulmonary arterial flow acceleration time and shortens right ventricular isovolumic relaxation time, which means that it reduces the Pulmonary Arterial Pressure
Clinical effects and safety of different strategies of intravenous diuretics in acutely decompensated heart failure

A randomised clinical trial

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ICA-SEMES Research Group, Spain
Results

- **Multicentre, randomised, parallel-group study.**
  - Group 1: furosemide administered by continuous infusion (10 mg/h; N=36)
  - Group 2: furosemide administered by boluses (20 mg/6h; N=37)
  - Group 3: furosemide administered by boluses (20 mg/8h; N=36)

- **Furosemide by perfusion achieved greater urine output**
  - Group 1 presented greater 24-hour diuresis (3,705 mL) than group 2 (3,093 mL) and group 3 (2,670 mL) (p<0.01)

- **Improvement of clinical signs and symptoms were observed in all groups, with no statistically significant differences in any of these 9 secondary clinical end-points**

- **Creatinine deterioration developed in 15.6%, hyponatremia in 9.2% and hypokalemia in 19.3%**
  - Differences among groups were only detected in hypokalemia (group 1: 36.3%; groups 2: 13.5%; group 3: 8.3%; p<0.01)
Diuretics in acute heart failure: is there a better strategy?

F. Caetano; I. Almeida; A. Fernandes; P. Mota; A. Botelho; A. Leitão Marques
Diuretics in acute heart failure: is there a better strategy?

F. Caetano; I. Almeida; A. Fernandes; P. Mota; A. Botelho; A. Leitão Marques

**Purpose:** compare patients with AHF according to the diuretic strategy used

**Methods:** 110 patients admitted for AHF

50.9% furosemide continuous perfusion

49.1% furosemide bolus

**Results - At Admission:**

- No differences regarding:
  - Gender, age, cardiovascular risk factors
  - History of coronary artery disease
  - History of chronic renal disease
  - HF etiology or precipitating factor

- **PERF** group met criteria of dire prognosis:
  - Lower systolic blood pressure *(p=0.011)*
  - More severe kidney lesion *(p=0.008)*
  - Lower LV ejection fraction *(p=0.046)*
  - Restrictive diastolic dysfunction *(p=0.032)*
Diuretics in acute heart failure: is there a better strategy?

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• **RESULTS – IN-HOSPITAL EVOLUTION:**

  - Needed **more aggressive therapeutic strategy**, with higher use of:
    - Vasopressors \( (p=0.003) \)
    - Inotropes \( (p=0.010) \)
    - Renal ultrafiltration \( (p=0.003) \)
    - Non invasive ventilation \( (p<0.001) \)

• **PERF GROUP:**

  - ↑ incidence of cardiorenal syndrome \( (77\% \text{ vs } 53\%; \ p=0.009) \)
  - ↑ increase in creatinine \( (70.0\pm93.4 \text{ vs } 30.7\pm47.0; \ p=0.006) \)

• **NO DIFFERENCES REGARDING:**

  - Renal function at discharge \( (\text{creat. } 141\pm86 \text{ vs } 132\pm71; \ p=0.860) \)
  - In-hospital mortality \( (19.6\% \text{ vs } 11.1\%; \ p=0.216) \)
  - Follow-up mortality or readmission for AHF

**CONCLUSIONS:** despite the severity of clinical presentation of patients treated with furosemide perfusion, they had the same in-hospital mortality and were discharged with similar renal function → **Furosemide perfusion might be a better option in hemodynamically unstable patients**