

HEART FAILURE DRUG DEVELOPMENT AT THE CROSSROAD

Brescia (Italy), September 01-02, 2016
Highlights

Introduction

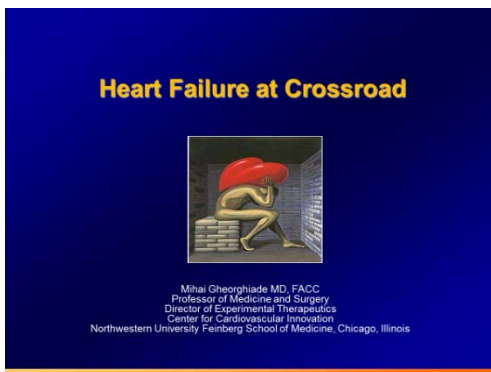


Prof. Nodari and Prof. Memo, the Chairmen of the Symposium, opened the congress by highlighting the scientific level of the meeting, they then passed on to present the program of this meeting, by stressing the point that this is the first Master course in Cardiology running in Brescia in collaboration with the University of Chicago represented by Prof. Gheorghiadu. The speakers concluded their talk by introducing the lecture on

Drug development in Heart Failure Disease and their colleague: Prof. Gheorghiadu from Chicago (USA).

To follow the presentations of this congress, click on the link below:

<http://www.fondazione-menarini.it/Archivio-Eventi/2016/Master-Course-on-Global-Research-Training-Program-in-Drug-Development-for-Heart-Failure/Materiale-Multimediale> ... and, after having logged in, enter in the multimedia area.



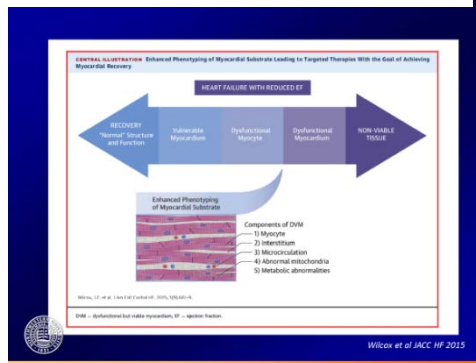
Drug Development for Worsening Heart Failure: Unmet Need

Prof. Gheorghiade from Chicago, (USA), in his lecture about the drug development for worsening Heart Failure, pointed out the increase of people suffering from HF and despite of drugs used for HF treatment, the majority of these patients are worsening. Most patients have normal blood pressure levels, without any particular complication at discharge, but despite of this we have a very high post-discharge mortality

rate, between 15% and 30%. The speaker pointed out the fact that this result is unacceptable, also taking into account that a lot of money has been spent in drug development in the last past years. Prof. Gheorghiade went onto present published data from the main scientific papers on the new strategies to be implemented in new drug development. In his conclusion the speaker pointed at the importance of starting immediately and working into the future, putting the heart at the core of "Heart Failure" and working on myocytes and their metabolism.

Chronic Heart Failure: Unmet Need

- Millions of patients worsening HF in spite of all available therapies often resulting in hospitalizations
- Majority are hypertensive or normotensive at presentation.
- Vast majority improve with diuretic therapy and discharged with minimum signs and symptoms.
- Despite in-hospital improvement and provision of guideline direct therapy, **post-discharge mortality and hospitalization are as high as 15% and 30%**, respectively, within 60 to 90 days post-discharge.
- Approximately 50% of patients have preserved EF for which there are no evidence-based therapies.
- Post-discharge event rate has not changed in the last 15 years.



- **Why do we have no new drugs for this condition despite a lot of time and money that we have spent?**
- **What does putting the Heart at the core of Heart Failure mean?**
- **How is it possible to go on with myocardial recovery?**
- **Which are the main metabolic abnormalities in the myocardium tissue?**
- **How important is targeting Mitochondria in HF treatment strategy?**
- **Which are the main Mitochondrial Functions in the Health and Diseased Myocardium?**

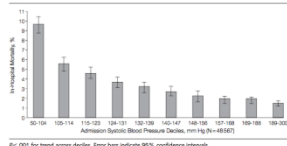
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Clinical Profile and Prognostic Value of Blood Pressure.

SBP at admission - predictor for mortality

Figure. In-Hospital Mortality Rates by Admission Systolic Blood Pressure Deciles (n = 48,967)

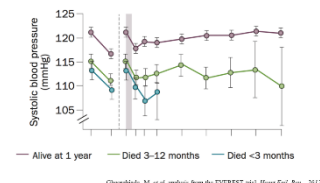


Chengzhi, M, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA, 2009.

Dr. Antohi from Bucharest, Romania, talked about this topic, underling the importance of monitoring the SBP changes in hospitalized patients, in order to stratify patients in a mortality risk ratio in post discharge time. The speaker presented the hypotesis, rationale, objectives and methods given for this posthoc analysis of the ASTRONAUT trial, more in particular of the patients enrolled in

the study placebo arm. The main expected result of this analysis is the linear relationship between SBP and outcome/quartile variation of correlation with outcome. In conclusion of this presentation Dr. Anthoi also presented the main clinical implications linked with this hypotesis.

SBP after hospitalization



Chengzhi, M, et al. analysis from the TYRIST trial. Heart Fail Rev., 2017

- What are the SBP levels to be achieved in HF patients?
- What are the main clinical implications of the posthoc analysis of placebo arm in ASTRONAUT trial?
- What are the methods of analysis performed in the posthoc ASTRONAUT trial analysis?
- What are the expected results?

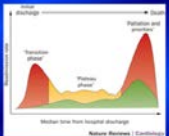
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Prognostic Significance of Serum Sodium Trajectory among Patients Hospitalized for Worsening Chronic Heart Failure Enrolled in ASTRONAUT Trial

Specific Aim:

- We want to determine the prognostic significance and associated clinical profile of early post-discharge serum sodium trajectory among patients hospitalized for worsening chronic heart failure enrolled in the ASTRONAUT trial.



Dr. Correale from Foggia (I) addressed this topic pointing out the importance of treating patients with hyponatremia, suffering from HF. The speaker presented the project of a posthoc analysis of hyponatriuremic patients enrolled in the ASTRONAUT trial. With the aim to determine the

prognostic significance and the clinical profile of post-discharge serum sodium trajectory among patients hospitalised for worsening chronic heart failure enrolled in the ASTRONAUT trial, Dr. Correale described the study methods and the expected results of this study.

Hypothesis section:

(1) Primary predictor: *change in serum Na level from baseline to 1 month post-randomization.*

This will be assessed via:

- Categorical analysis based on baseline and 1 month sodium levels: 4 groups (stable low, decreasing, stable high, increasing). Specifically, groups will be defined presence/absence of hyponatremia at baseline and 1 month.

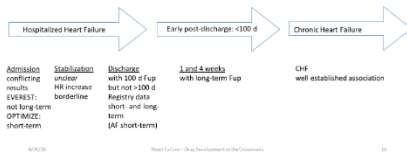
- What are the proposed methods of analysis in the posthoc study?
- What is the main Hypothesis of this posthoc study, presented by the speaker?
- What are the study endpoints?

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Prognostic Significance of Heart Rate.

Association of heart rate with outcomes



Dr. Düngen from Berlin, Germany talked about this topic and its impact on disease progression. The speaker started his speech by pointing out how easy it is to take the pulse rate, but at the same time how under evaluated this measure is. In his speech Dr. Düngen presented a study project based on a posthoc analysis of 948 ASTRONAUT HHF patients

that are not in atrial fibrillation/flutter or are not pacemaker dependent. The Heart Rate levels, analysed in this group of patients, seems to be an easily accessible therapy target which would improve the outcome in patients hospitalized for HF, the speaker pointed this out as the conclusion of his presentation.

Objectives

- To describe the Patient Characteristics by Baseline Resting Heart Rate Quartile
- To describe Heart Rate Trajectory during hospitalisation and Early Post Discharge Phase
- To evaluate All-cause Mortality by Continuous Heart Rate Change (>70/min and <70/min)
- To describe All-Cause Mortality by Baseline and 1-Month Follow-up Heart Rate Quartile
- To describe the clinical course of heart rate for patients enrolled for hospitalized HF after initial stabilization
- To compare patients with sinus rhythm and atrial fibrillation

- **What are the main associations between heart rate and outcomes?**
- **What are the main correlations between HF and HR in hospitalized patients?**
- **In ASTRONAUT trial does heart rate on admission correlate with all-cause of mortality?**
- **In the ASTRONAUT trial there was a correlation between HR at discharge and mortality at 100 days?**
- **In the ASTRONAUT trial what is the main correlation between hospitalized patients for HF and atrial fibrillation?**

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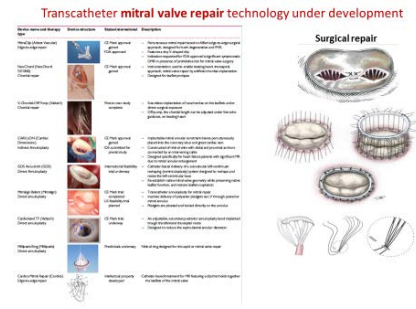
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Interventional treatment of Heart Failure.

It is an Epidemic

- Estimated that over 5 million Americans have HF
- Estimated 500,000 new cases per year
- Within 5 years, half of those diagnosed will be dead
- Over 1 million hospitalizations per year with HF as primary diagnosis
- Most common reason for hospitalization in those >65 years old
- 85% of HF cases are in adults 65 and older
- Heart failure is 4th in a list of quality of care initiatives in vulnerable older adults

Prof. Romeo from Rome (Italy) in his presentation talked about heart failure and its interventional treatment. Starting from the main topics linked with the prevalence of disease and its mortality rate, the speaker stressed the epidemic status of HF in the world despite the pharmacological tools developed in last 20 years. In order to



better understand this phenomenon, Prof. Romeo went deep into describing one of the main important diseases responsible for the future development of HF: the mitral regurgitation. A very underestimated disease, the speaker

pointed out and one of the main causes of HF as its natural evolution. The main part of the lecture was spent in describing the interventional techniques applied in the treatment of MR: the Mitraclip technique. Finally, Prof. Romeo presented data taken from his clinical experience, the so called MitraClip Therapy: Tor Vergata Experience. The speaker concluded his lecture presenting data about the first-in-man Trans-catheter mitral valve implantation, performed by his team at Tor Vergata Hospital.



- 25th of march 2015, 1st patient treated
- Transapical approach
- Functional MR
- Ischemic cardiomyopathy
- No extracorporeal circulation
- 2 months of follow up: good valvular function and trace of residual mitral regurgitation
- 15 mmHg of LVOT gradient, significant clinical benefit, characterized by improvement in symptoms, NYHA functional class and quality of life

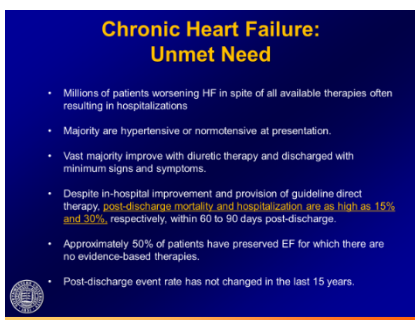
J Cardiovasc Med (Hagerstown). 2016 Feb;17(2):85-91.

- **What are the main demographic data of the Mitraclip therapy: Tor Vergata Experience?**
- **What are the main results obtained with MitraClip technique in Tor Vergata Hospital?**
- **What are the main data presented by the speaker about the implantation of a mitral valve via the Transapical approach at the Tor Vergata Hospital in 2015?**

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Round Table on ‘Drug Development for Heart Failure: Unmet Needs.’



A very interesting round table has been performed in connection with people from around the world. Prof. Gheorghiade started his intervention, pointing out the very big problem, that is: worsening heart failure, despite the billions of dollars spent in non-sense-clinical trials gaining no results in terms of better outcome for patients with HFpEF. What is the issue? The meeting started when Prof. Gheorghiade proposed this question to his colleagues that took part in this round table. One point highlighted by all the speakers was linked

with the necessity to grow awareness around this entity: the worsening chronic heart failure, as a new disease which is very different from the classic heart failure syndrome. The One big dream: have the right specific drug for a specific disease. The drugs delivered till now are capable of relieving the symptoms, but the underlying disease goes forward without being stopped. The key point is to study the causes which determine the progression of the disease and deliver drugs capable on acting on these causes. One other big issue discussed in the meeting, dealt with the necessity to select the right site to be included in the clinical studies.

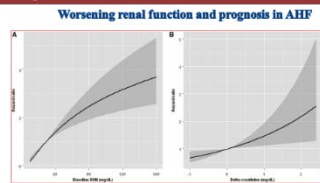
- **What is worsening Heart Failure, is it dealing with worsening of symptoms or with worsening of the mechanism of disease?**
- **How do we increase public awareness of the disease, or more specifically pointing to the public payers?**
- **How to define from a regulatory point of view, Chronic Heart Failure as a new entity of disease?**
- **How to deliver new drugs acting at the metabolic myocytes level?**
- **How to characterize Heart Failure patients from a phenotyping and a genotyping point of view?**
- **How to perform the site selection for clinical trial in chronic heart failure?**

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Changes in Renal Function During Hospitalization and Soon After Discharge and Outcomes.

Background



Renal Function Trajectories and Clinical Outcomes in Acute Heart Failure

Michael M. Gheorghiade, MD, Doreen Pasternak, PhD, Hans L. Hillege, MD, PhD, George A. Mensen, MD, Barry M. Massie, MD, Beth A. Davison, PhD, Piotr Ponikvarski, MD, Marco Metra, MD, John E. Teerlink, MD, John G.F. Cleland, MD, Howard C. Dittrich, MD, Christopher M. O'Connor, MD, Gad Cotter, MD, Adrian A. Voors, MD
Circ Heart Fail. 2014;7:59-67.

Dr. Monitillo from Bari, Italy, spoke about the relationship between renal function and HF hospitalization. More in particular the speaker addressed the topic of the correlation between magnesium serum levels and the outcome of patients hospitalized for Acute Heart Failure. The data taken from

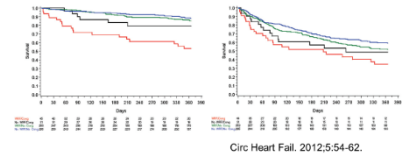
Discussion

Worsening renal function and congestion

Is Worsening Renal Function an Ominous Prognostic Sign in Patients With Acute Heart Failure?

The Role of Congestion and Its Interaction With Renal Function

Marco Metra, MD; Beth Davison, PhD; Luca Bettari, MD; Hengrui Sun, MD; Christopher Edwards, BS; Valentina Lazzarini, MD; Barbara Piovarelli, MD; Valentina Cambelli, MD; Silvia Bugatti, MD; Carlo Lombardi, MD; Gad Cotter, MD; Livio Dei Cas, MD



Circ Heart Fail. 2012;5:54-62.

literature are controversial and in order to have a better understanding whether or not there is such a correlation, Dr. Monitillo presented a new posthoc analysis project, by using the ASTRONAUT published data. The main endpoint is to describe characteristics and outcomes of HFrEF patients with reduced EF in respect to early post-randomization SCr trajectory and the occurrence of WRF.

- What is the relationship between renal dysfunction and heart failure?
- How can renal function during hospitalization in patients admitted for worsening heart failure change?
- What is the Aliskiren' effect on postdischarge mortality in patients hospitalized for heart failure?
- Is worsening heart failure an ominous prognostic sign in patients with Acute Heart Failure?

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Clinical Profile and Prognostic Value of Anemia at Discharge.

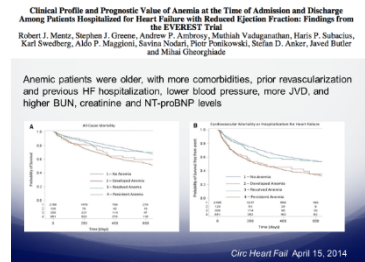
Prevalence Of Anemia in HF patients

- Anemia is highly prevalent in ambulatory heart failure (HF)
- All currently available data indicate that anemia is common in HF populations, with the majority of studies indicating prevalence 20%, and many studies indicating prevalence of nearly 50%.
- Anemia appears to be consistently more highly prevalent in HF patients with advanced age, more severe limitations in functional capacity and greater severity of co-morbid chronic kidney disease in both acute and chronic HF populations, and in patients with impaired or preserved systolic function

Yu-De Tang Heart Fail Rev (2008) 13:387-392

Dr. Petroni from L'Aquila, Italy, presented data on the relationship between anemia and the outcome of patients with heart failure. Patients with HF are also prone to develop an Iron Deficiency, the speaker pointed out and the presence of iron deficiency can put the HF patient at a higher risk of mortality. Another point the speaker highlighted concerns about the correlation

between quality of life and presence of anemia in patients with HF. Based on these data Dr. Petroni presented a new posthoc analysis project, by using the ASTRONAUT published data. The main endpoint is to investigate the correlations between quality of life and anemia in patients with HF.

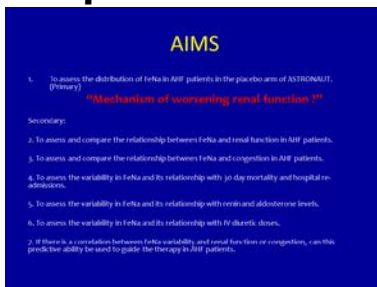


- **What are the expected results of the posthoc analysis project presented by the speaker?**
- **What are the key point of the relationship between Iron deficiency and HF?**
- **What is the prevalence of anemia in HF patients?**

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Prognostic Value of Fractional Excretion of Sodium in Patients Hospitalized for Heart Failure.



AIMS

1. To assess the distribution of FeNa in AHF patients in the placebo arm of ASTRONAUT. (Primary)

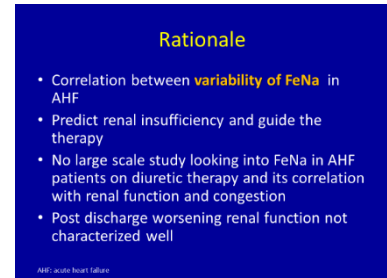
"Mechanism of worsening renal function"

Secondary:

2. To assess and compare the relationship between FeNa and renal function in AHF patients.
3. To assess and compare the relationship between FeNa and congestion in AHF patients.
4. To assess the variability in FeNa and its relationship with in-day mortality and hospital re-admissions.
5. To assess the variability in FeNa and its relationship with creatinine and aldosterone levels.
6. To assess the variability in FeNa and its relationship with IV diuretic doses.

2. If there is a correlation between FeNa variability and renal function or congestion, can this provide low ability to guide the therapy in AHF patients.

Dr. Shahbaz from Blaine, USA, presented data on this topic, taking into account the correlation between fractional sodium excretion and HHF patients. The speaker pointed out that FeNa is one of the markers of diuretic therapy. This marker is useful in patients with acute renal failure in order to better detect the sodium renal handling and as a



Rationale

- Correlation between **variability of FeNa** in AHF
- Predict renal insufficiency and guide the therapy
- No large scale study looking into FeNa in AHF patients on diuretic therapy and its correlation with renal function and congestion
- Post discharge worsening renal function not characterized well

AHF: acute heart failure

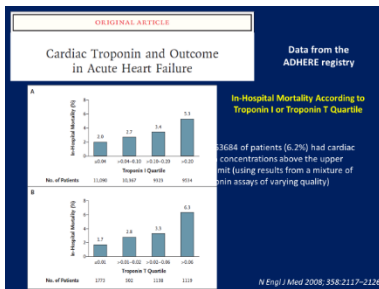
consequence, predict a new state of renal insufficiency and guide the therapy. The speaker presented a new posthoc analysis project, by using the ASTRONAUT published data. The main endpoint is to assess the distribution of FeNa in AHF patients in order to detect one of the mechanisms of worsening renal function.

- **What are the main analysis plan selection criteria chosen by the speaker for his posthoc analysis?**
- **What are the main aims of this project presented by the speaker?**
- **What is the rationale of this project?**

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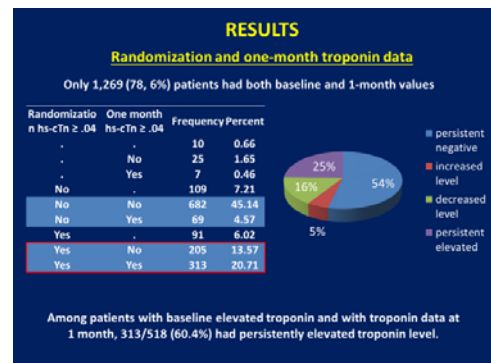
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High Sensitive Cardiac Troponin Plasma Level and Outcome



Dr. Triggiani from Brescia, Italy, spoke about this topic, pointing out at the mechanism linking this biomarker to the outcome of patients with HF. The speaker also presented data about the main causes leading to the release of troponin in HF patients, more in particular in those patients

hospitalized for worsening HF. The lack of data about the correlation between changes in hs-cTn during hospitalization and the patients risk stratification united with the lack of studies exploring the prognostic significance of ongoing cardiac injury during early post-



discharge period, gave the opportunity to the speaker to implement a posthoc project using the ASTRONAUT data, with the intention to explore the possible association between in-hospital Troponin elevations and the outcome in HHF patients. In the last part of his talk the speaker presented the main data produced in this posthoc analysis, pointing out the importance of measuring troponin I during the vulnerable phase as a practical means of risk stratification.

RESULTS: Clinical outcomes by baseline and one-month troponin I elevation

Endpoints (1-year)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
Baseline troponin I elevation		
All-cause death	1.58 (1.24-2.01), p<0.001	1.23 (0.95-1.59), p=0.113
CVM/HHF	1.34 (1.13-1.59), p<0.001	1.11 (0.93-1.33), p=0.257
1-month troponin I elevation		
All-cause death	2.28 (1.73-3.01), p<0.001	1.81 (1.35-2.45), p<0.001
CVM/HHF	1.86 (1.53-2.26), p<0.001	1.43 (1.16-1.77), p<0.001

*Adjusted for age, gender, race, geographic region, ischemic heart failure etiology, New York Heart Association Class III/IV, ejection fraction, systolic blood pressure, heart rate, NT-proBNP, serum sodium, blood urea nitrogen, serum creatinine, QRS duration, atrioventricular conduction, past medical history (prior MI, coronary artery disease, atrial fibrillation, diabetes, chronic obstructive pulmonary disease), and baseline medications (ACE/ARB, beta-blocker, mineralocorticoid receptor antagonist, digoxin, implantable cardioverter-defibrillator, cardiac resynchronization therapy)

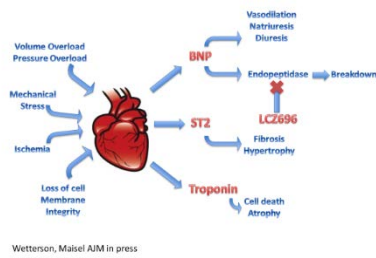
The association between 1-month troponin elevation and outcomes was not influenced by presence/absence of baseline troponin elevation (P for interaction ≥ 0.69).

- What is the aim of the posthoc analysis project presented by Dr. Triggiani?
- What is the correlation between Troponin changes and patients risk stratification?
- What is the origin of the circulating troponin T?
- What are the posthoc analysis methods presented by Dr. Triggiani?
- What are the main results of this posthoc analysis, presented by the speaker?

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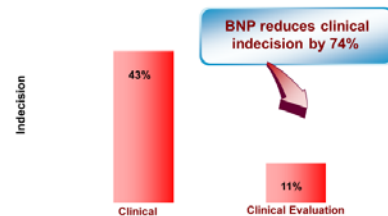
The Role of Biomarkers in HF



Prof. Maisel from San Diego, USA in his presentation talked about biomarkers in HF as a guide for clinicians. The speaker started his lecture, highlighting the dramatic epidemic state of HF in all the world. Based on the data published from the main clinical studies runned on HF patients, Prof. Maisel analysed the role of BNP, PCT, Troponin and ST2. Speaking about any of these biomarkers, he

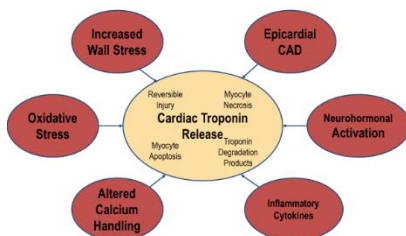
examined in depth their main aspects as indicators of disease and predictors of outcome. The speaker also talked about the problems related with the different interpretations of these biomarkers, more in particular he spoke about the relationship between BNP and NT-proBNP and drug therapy, the role of PCT in patients with heart failure and lung infection and its role as predictor of short term mortality, the role of Troponin

Clarification of Diagnosis & BNP



and its meaning in acute heart failure patients, the role of sST2 and its strong relationship with mortality. After this very complete review on biomarkers and their role in diagnosis and prognosis of patients with HF, the speaker concluded his lecture highlighting that biomarkers can be very useful in patients' diagnosis but need to be used by doctors that take care in performing physical examinations of their patients.

Cardiac Troponins
Overview and Mechanism of Troponin Release



- Where do biomarkers fit in?
- What are the objectives of biomarkers testing in heart failure?
- What are the standard diagnostic biomarkers for acute heart failure?
- What is the main use for PCT in HF patients?

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Early Drug Development in Heart Failure.

Early Drug Development in Heart Failure

The 2016 Paradigm Shift

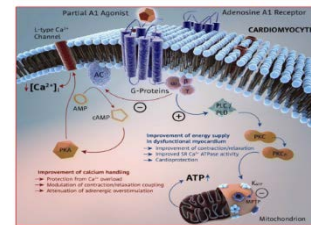
- To garner high enthusiasm for extensive and expensive pre-clinical and translational development, a new drug must strive to achieve some or all of the following characteristics:

1. Hemodynamically neutral
2. The heart is the primary target
3. Produce "lasting" functional benefits
4. Produce "lasting" structural benefits
5. Improve "quality of life"

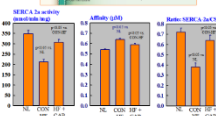
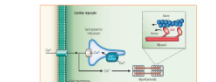


Prof. Sabbah from Detroit, USA presented very interesting data about the future perspectives for treatment strategies in Heart Failure. The new drugs have to be hemodynamically neutral, targeting at first the heart, producing lasting functional and structural benefits and improving quality of life. More in particular Prof. Sabbah spoke about vepoloxamer and its effect on LV function, on capadenosan, a partial adenosine A1- receptor agonist and its effect in animal models studies, on elamipretide, its association with cardiolipin and its effect on mitochondrial function. In conclusion, the speaker pointed that the new drugs for heart failure have to be hemodynamically silent, providing added value over SOC, translatable end- points and capable to manage comorbidities.

Partial Adenosine A1-Receptor Agonist



Mechanism of Action SR Calcium Handling in HF Dogs

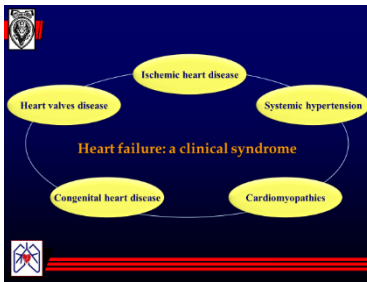


- What is the most suitable animal model for testing drug efficacy?
- What is the effect of vepoloxamer on LV function in animal model?
- What are the main hemodynamic characteristics of Capadenosan tested in dogs with heart failure?
- What is the mechanism of action of SR Calcium handling in HF dogs?
- What is the main effect of elamipretide in HFrEF dogs?

To reply to these and other questions just click on the link below:

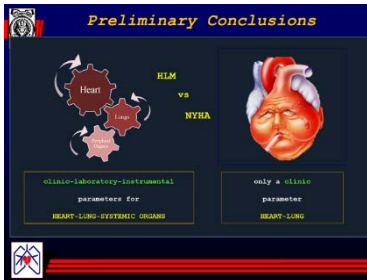
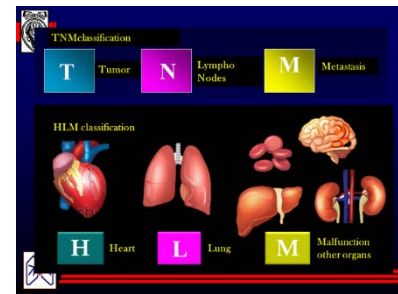
<http://www.fondazione-menarini.it/Archivio-Eventi/2016/Master-Course-on-Global-Research-Training-Program-in-Drug-Development-for-Heart-Failure/Materiale-Multimediale> ... and, after having logged in, enter in the multimedia area.

A New Proposed Method for Heart Failure Staging.



where H stands for Heart, L for lungs and M for malfunction of other organs.

Prof. Fedele from Roma, Italy, presented a new method for staging HF patients. Heart Failure is a syndrome than a disease, the speaker pointed out and as a syndrome involves more organs other than the heart: lungs, liver, kidneys, brain and blood. In this view a new classification has been implemented, the so called HLM classification, where H stands for Heart, L for lungs and M for malfunction of other organs. The speaker spent the main part of the presentation in presenting this new method of staging, based on AIM study, an ongoing study performed by his medical team. In the last part of his speech, Prof. Fedele presented also some preliminary data of this study and the prognostic power of the HLM classification applied to these data.

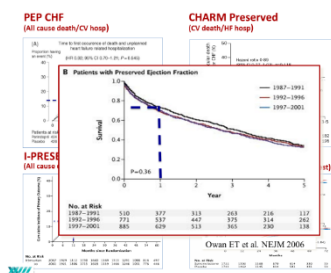


- What are the staging levels for each organ?
- What are the preliminary results of the AIM study?
- What is the statistical dependence's level of HIM variables?
- What the prognostic power for each HLM variable?

To reply to these and other questions just click on the link below:

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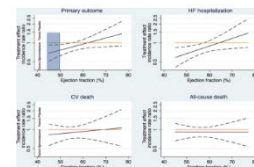
Developing Therapies for Heart Failure with Preserved Ejection Fraction



Prof. Senni from Bergamo, Italy, spoke about HF with preserved ejection fraction, starting from the indications given by the HFpEF trials. The speaker reviewed the results of the main clinical trials on HF, with particular attention to the cardiovascular event rate, the relevance of hospitalization and NPs. Another major point of discussion regarded the issues leading to the misdiagnosis of disease, as the lack of applying the diagnostic criteria for HFpEF present in the guidelines, in the

Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction

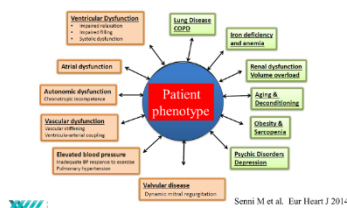
Scott D. Solomon¹, Brian Claggett¹, Eldrin F. Lewis², Akshay Desai¹,INDER ANAND³, Nancy K. Sweitzer⁴, Eileen O'Mara⁵, Samir J. Shah⁶, Sohaib M. Khan⁷, Jerome L. Pfeiffer⁸, George Sopko⁹, Bertram Pitt¹⁰ and Marc A. Pfeffer¹, for the TOPCAT Investigators



Eur Heart J 2016

leading to the misdiagnosis of disease, as the lack of applying the diagnostic criteria for HFpEF present in the guidelines, in the

HFpEF: Pathophysiology



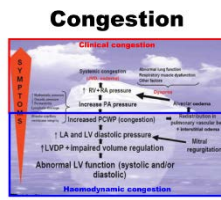
trials specifically designed for this pathology. The last part of his lecture was spent in presenting the pathophysiologic phenotype approach for HFpEF patients, more specific for these patients and able to open a new way: the molecular target for therapy. In conclusion the speaker pointed to the importance of this new approach able to identify targeted therapies for heart failure phenotypes, instead of the old “one-size-fits-all” approach.

- What are the main causes of mortality in HFpEF based on the Olmsted County study population?
- What are the main causes of HF misdiagnosis?
- Why the speaker recommended to enrol patients in the studies, during hospitalization?
- What is the main characteristic of HFpEF from a pathophysiologic point of view?
- Why is the phenotype characterization for HF patients with preserved ejection fraction important?

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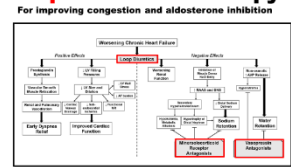
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Neurohormonal Inhibition for Heart Failure: End of an Era



Prof. Sato from Kanagawa, Japan, in his very interesting talk spoke about: congestion from a clinical point of view, the Aldosterone level at admission and the effect of the infusion of carperitide - an atrial natriuretic peptide - in these patients. The speaker pointed to the effects of the angiotensin-neprilysin inhibition compared to ACEI effects, highlighting that we are at the down of a new era in HF therapy. Prof. Sato spent the main part of his presentation in presenting data on mineralcorticoid receptor antagonists and more in particular on the effects of high dose spironolactone administration in these patients. In conclusion Prof. Sato highlighted the importance to protect heart by improving congestion via RAA inhibition.

Triple diuretic therapy



Expert Review of Cardiovascular Therapy 2015; 13: 799-809

Summary

Still we should pay attention to the RAA inhibitions in terms of management of HHF

RAA inhibition (Dose/Timing)

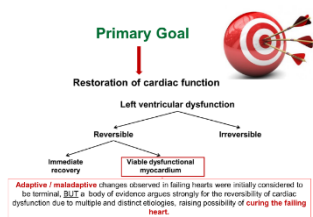
is important to protect heart with improving congestion for the coming of a new era

- Why is important to treat congestion from the speaker point of view?
- What are the main effects of carperitide?
- What are the main effects of high dose of spironolactone in patients with ADHF?
- What is the triple diuretic therapy presented by the speaker?

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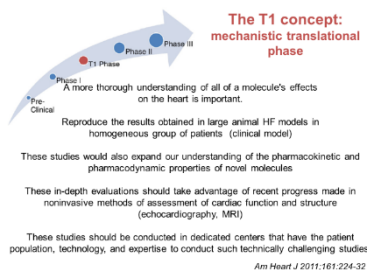
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Mitochondria in Heart Failure: an essential target.

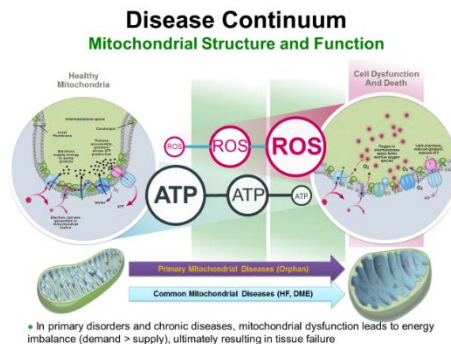


Byronia, Circ Heart Fail. 2012

the restoration of cardiac function, via the restoration of the myocardial function also in presence of clear signs and symptoms of dysfunction. This new approach passes through the restoration of the mitochondria functions.



Prof. Nodari, Brescia, Italy, spoke about mitochondria as a new target for HF patients' treatment. The speaker started her speech highlighting the limits of the traditional therapeutic approach of HF, more in particular in patients affected by HF with preserved EF. The primary goal of the HF therapy should be the



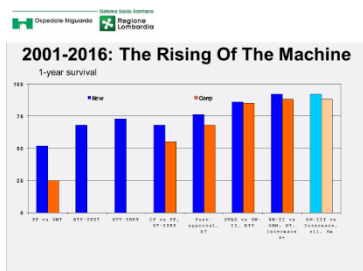
The speaker presented data from some rCTs on the effects of the new drugs targeting the mitochondrial dysfunction. In conclusion Prof. Nodari highlighted the need for a better characterization and more studies on these new molecules with the aim to improve the management of patients affected by HF with preserved EF.

- What is the so called “T1 concept: mechanistic translational phase”?
- What are the main characteristics of the partial adenosine A1-receptor agonist?
- What are the main characteristics of Elamipretide on myocytes metabolism?
- What are the main metabolic abnormalities in patients with HF?
- Why mitochondrial dysfunction can be a therapeutic target in failing HF?

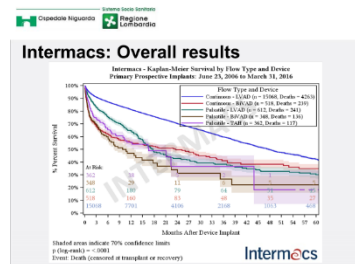
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Ventricular Assist Devices



highlighted. The main part of this presentation was spent in describing the data published from the most important trials on IVAD, performed in these years. Prof. Frigerio highlighted that, despite the improving in saving life in emergency conditions, it is



necessary to get to new targets, in terms of better outcomes not only on mortality, but also on complications rate and time to HT. The speaker pointed out that the device plays a major role in this process. In the last part of her presentation, Prof. Frigerio presented data on a new device, the so called “HeartMate III”. In conclusion the speaker highlighted the necessity to improve Pt. selection, patient-device matching, hemodynamic optimization in pre-surgical phase, Pt. and caregiver education, medical therapy

HeartMate III: First Clinical Results

- 50 pts at 10 Centers
- Observational (benchmark Intermacs)
- Transplant eligible and ineligible (27/23)
- Advanced Heart Failure, NYHA III/IV (26/24)
- 88% Intermacs 2 to 4
- **Survival: 98% at 30-days, 92% at 6 months, 81% at 1-year**

Zimpfer D et al. Eur J Cardiothor Surg 2016; doi:10.1093/ejcts/ezw169
Nataf J et al. J Am Coll Cardiol 2015; 66:23
Krabalovich T et al. ISHLT meeting, Washington 2016

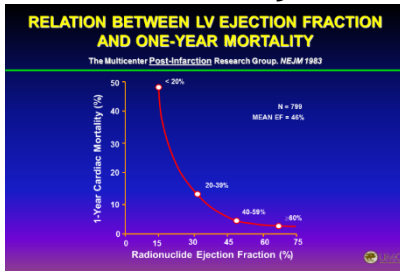
and access to lifelong care in order to improve outcome.

- What is the outcome in patients treated with inotropes during AHF hospitalization?
- What are the contemporary outcomes of patients affected by refractory HF?
- What is the Niguarda experience from 2006 to 2016 in LVAD patients?
- What are the main characteristics of the devices available on the market?
- What are the main characteristics of HeartMate III device?

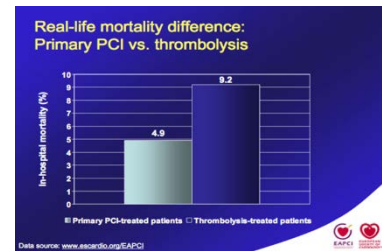
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Percutaneous Revascularization in Severe Viable Left Ventricular Dysfunction



Prof. Indolfi from Catanzaro, Italy, spoke about this topic by presenting interesting data on ventricular dysfunction and revascularisation. The speaker presented very impressive data on 1-year mortality in correlation with LV ejection fraction and the effects of primary PCI in comparison with thrombolysis.



The main part of this lecture was spent in describing the myocardial pathological conditions in case of dysfunction. The speaker examined in depth the correlation between subendocardial flow and ischemia. More in particular Prof. Indolfi spoke about hibernating myocardium and the possibility to gain left ventricular function by applying percutaneous coronary interventions with the 2^o DES generation.

CONCLUSIONS

Percutaneous revascularization in the setting of acute myocardial infarction remains the best strategy to increase left ventricular function and to reduce the mortality rate.

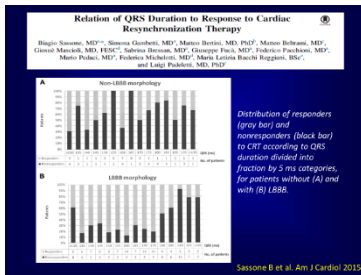
In chronic, but viable, left ventricular dysfunction, percutaneous coronary interventions with the 2nd generation of DES increase the left ventricular function and therefore affects the long term prognosis in patients with hibernated myocardium.

- What are the main results in the only one comparison study between revascularization and CABGS in patients with multivessel coronary artery disease?
- What is the role of the subendocardial flow in determining regional myocardial contractions?
- Why is the revascularization in patients affected by myocardial hibernation so attractive from the speaker point of view?

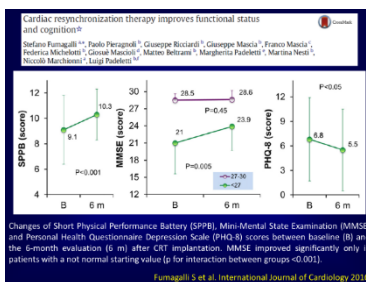
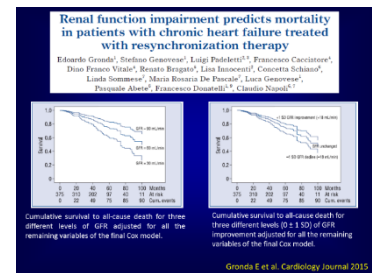
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Cardiac Resynchronization Therapy and Implantable Cardioverter Defibrillator in Heart Failure.



Prof. Padeletti from Milano, Italy, spoke about this topic by presenting interesting data on cardiac resynchronization therapy. The speaker reviewed the main characteristics of candidate patients for this therapeutic procedure and described the main results of CRT in correlation with the pathophysiological conditions present in the implanted patients. More in particular the speaker spoke on Bundle pacing and its effect on LV function and highlighted the crucial role played by the intrinsic right ventricular conduction for optimal CRT delivery. In the last part of his speech Prof. Padeletti presented data on moxonidine in patients with Heart Failure, in order to highlight the differences between response and outcome. In conclusion Prof. Padeletti highlighted the powerful effect of this type of treatment in slowing the disability and frailty in heart failure patients.



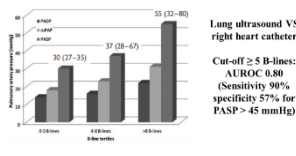
- What are the main indications for CRT in patients presenting with HF?
- What is the prognostic Impact of QRS Axis Deviation in Patients Treated with Cardiac Resynchronization Therapy?
- What is the correlation between renal function and CRT?
- Why in CRT the two concepts of response and outcome are very different one from the other?

To reply to these and other questions just click on the link below:

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Lung Ultrasound Imaging

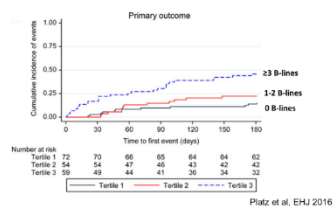
Utility of lung ultrasound in predicting pulmonary and cardiac pressures



Platz et al., Eur J Heart Fail 2012

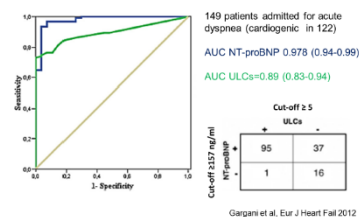
utility of lung ultrasound in predicting pulmonary and cardiac pressures, its correlation with the radiological signs of congestion by lung ultrasound in HFrEF outpatients

Prognostic value of pulmonary congestion by lung ultrasound in HFrEF outpatients



Prof. Ambrosio from Perugia, Italy, spoke about this topic by presenting interesting data about the correlation between Lung ultrasound and diagnosis and prognosis of HF patients. Starting from data given from the literature, the speaker discussed about the diagnostic impact of Lung ultrasound in HF patients, more in particular Prof. Ambrosio highlighted the utility of lung ultrasound in predicting pulmonary and cardiac pressures, its correlation with the radiological signs of congestion and the main echo indicators of Chronic HF. The last part of the lecture was spent in presenting data on the prognostic value of Lung Ultrasound technique. In conclusion the speaker highlighted that Lung ultrasound is a simple and reliable tool, useful in AHF diagnosis, useful in monitoring congestion in HF patients and a good short-term prognostic predictor.

AHF diagnosis: comparison with natriuretic peptides



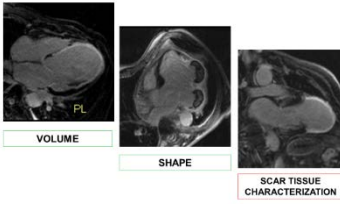
- What is the classical clinical use of Lung ultrasound?
- Why the Lung ultrasound technique is a new tool for the cardiologist from the speaker point of view?
- What are the results in Lung ultrasound application for the evaluation of pulmonary congestion in HF outpatients?
- Is it possible to use the Lung ultrasound technique in AHF diagnosis?

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Cardiac MRI

Cardiac Magnetic Resonance



Prof. Lombardi from Milano, Italy, spoke about this topic by presenting data on MRI technique applied to patients affected by different forms of Heart Failure. The speaker talked about MRI performed in patients affected by many cardiological diseases, like MI, LV remodelling and surgical ventricular reconstruction and presented also data about the role of scar tissue, as assessed by CMRI, in predicting ventricular response

The role of scar tissue as assessed by CMR in predicting ventricular response to Surgical left Ventricular Reconstruction in ischemic heart failure patients

S. Castelvécchio, G. Carei, L. Menicanti, F. Ambrogi, M. Lombardi

To investigate whether the assessment of post-infarct myocardial scar extent and distribution by LGE-CMR may predict postoperative cardiac function in patients with ischemic HF treated by SVR

Just submitted

Changes in CMR and clinical variables in the study population (N=59)

Variable	Pre-SVR	Post-SVR	p value
LVEDVI, ml/m ² [mean, SD]	118±36	94±27	<0.001
LVESVI, ml/m ² [mean, SD]	85±34	59±23	<0.001
LVEF, % [mean, SD]	29±9	39±11	<0.001
LVSVI, ml/m ² [mean, SD]	33±10	35±11	0.124
Lvmass(I), ml/m ² [mean, SD]	103±24	89±19	<0.001
RVEDVI, ml/m ² [mean, SD]	51±16	57±17	<0.001
RVESVI, ml/m ² [mean, SD]	22±10	25±11	0.002
RVEF, % [mean, SD]	56±11	58±11	0.428
RVSVI, ml/m ² [mean, SD]	29±10	32±10	0.006
LVDISI [mean, SD]	0.37±0.09	0.53±0.50	<0.015
NT-proBNP, ng/l [mean, SD]	2291±2319	1479±1480	<0.005

to surgical left ventricular reconstruction in patients affected by ischemic heart failure. In conclusion Prof. Lombardi highlighted the role of CMRI in the management of patients affected by HF, as a flexible tool for assessing parameters which are already in use and in selected subgroups of patients as the first choice imaging approach.

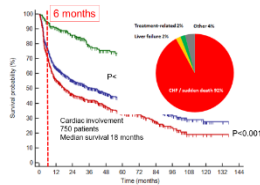
- What are the main results of the study performed by Prof. Lombardi and his team?
- What is the role of MCRI in patients affected by surgical ventricular reconstruction?
- What is the design of the study presented by the speaker?

To reply to these and other questions just click on the link below:

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The Amyloid Cardiomyopathy

Survival of 584 patients with AL amyloidosis diagnosed at the Pavia Amyloid Center



Prof. Perlini from Pavia, Italy, presented data taken from the literature and ongoing studies performed by his team. In the first part of his presentation the speaker described the main characteristics of this disease, and the main forms involving the heart, highlighting that the prognosis depends on cardiac amyloidosis type closely related to the cardiotoxicity of the amyloidogenic light

chains. In the main part of his presentation, Prof. Perlini talked about the therapeutic tolls available for these patients and presented data taken from early phases' clinical studies performed

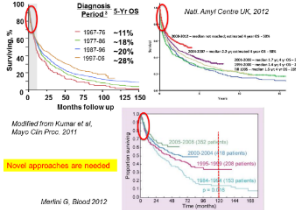
in patients affected by amyloidosis. In the last part of this lecture the speaker

highlighted the deep correlation between genotype/phenotype profile and the outcome of disease. In conclusion Prof. Perlini pointed to the necessity of an international collaboration in order to make progress in diagnosis, prognosis and therapy, taking in account that amyloidosis is a rare disease.

Cardiac Involvement in Amyloidosis



Improvement in survival in AL amyloidosis

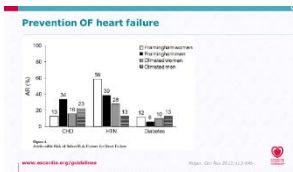


- What are the main causes of cardiac damage in patients affected by any form of amyloidosis?
- Is cardiac amyloidosis an “incurable” disease?
- What is the result produced by therapy development in AL amyloidosis at the Pavia Hospital, presented by the speaker?
- What are the three main forms of amyloidosis involving the heart?
- Are the mitochondria involved by the pathological mechanisms of disease?
- How is important the early diagnosis for the outcome of amyloid cardiomyopathy?

To reply to these and other questions just click on the link below:

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Prevention in Heart Failure



Prof. Piepoli from Piacenza, Italy, spoke about this topic by presenting data on the prevention's strategies to be applied in patients affected by Heart Failure. The speaker divided these strategies into two groups, the first one to be applied for HF and the others one to be applied for prevention of

HF complications. More in particular the speaker highlighted the need for implementing tailored strategies for hospitalized patients,

Cardiovascular prevention IN heart failure

Key message

- CHF prevention in HF patients should start as soon as possible, and requires a multifaceted integrated tactic.

- in-hospital
- discharge
- out-patient clinic
- primary care

Risk factor	Target level	Management goal
Smoking	No exposure to tobacco in any form	no tobacco
Diet	Low saturated fat intake (less than 7% of total energy), low sodium, potassium, calcium, fiber and other	healthy diet
Physical activity	At least 150 minutes a week of moderate-intensity (30 minutes for 5 days/week) or 75 minutes a week of vigorous-intensity (30 minutes for 3 days/week) or equivalent of moderate-intensity	see later
Body weight	Body mass index (BMI) 20-25 kg/m ² (normal weight) or 25-30 kg/m ² (overweight) or 30-35 kg/m ² (obesity) or 35-40 kg/m ² (severe obesity)	obesity paradox? 20-25 ?
Blood pressure	<130/80 mmHg	see later
Lipids	LDL-C <100 mg/dL (2.6 mmol/L) or <70 mg/dL (1.8 mmol/L) in patients with atherosclerotic cardiovascular disease	see later

characterized by a very high risk profile, a more heterogeneity in the clinical presentation of the disease and some specific issues, like statins therapy, specific physical activity, vaccination for influenza and others. In conclusion Prof. Piepoli pointed that Cardiovascular prevention is a life-long endeavour.

- What are the main procedures to be implemented in HF prevention from the speaker point of view?
- How is important the exercise training program in HF prevention?
- What are the main prevention's strategies to be implemented in HFrEF patients?
- When is necessary to start with a prevention's program in HF patients?

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These are only some of the topics addressed in the congress's sections

For a deeper knowledge on these topics, please visit the International Menarini Foundation web site where You can find all the speeches in their full version.

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