

Joint Meeting on  
7<sup>th</sup> INTERNATIONAL CONFERENCE ON HYPERTENSION AND HEALTHCARE  
&  
29<sup>th</sup> INTERNATIONAL CONFERENCE ON CARDIOLOGY AND HEALTHCARE  
June 10-11, 2019 Helsinki, Finland



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### Limits of pharmacological treatment in heart failure

Heart failure (HF) is the most common and deadliest syndrome in contemporary Cardiology. A poor prognosis, frequent re-hospitalizations and decreased quality of life is sadly still characterizing the patient with heart failure. Despite major advances in pharmacological and interventional treatment, heart failure remains a major health problem in all European countries. With a prevalence between 4,4% - 7% and an incidence between 2,5‰ - 44‰, HF tends to progress with the aging. If today there are estimated 15M patients with HF in Europe, by 2030 this number is expected to double. Main objectives of pharmacological treatment in heart failure are represented by: prevention of myocardial damage through optimal management of diseases that cause HF (coronary artery disease, valvular diseases, hypertension), preventing and slowing the ventricular remodeling process, treatment of associated comorbidities (such as diabetes mellitus, chronic kidney disease, atrial fibrillation, iron deficiency, etc), reduction of morbi-mortality, decreasing the number of re-admissions due to acute worsening of HF and improvement of clinical status, functional capacity and quality of life of patients with HF. The pharmacological treatment in HF with reduce LV ejection fraction is targeting the neuro hormonal systems involved in development and progression of this condition: the over activation of sympathetic nervous system (SNS), of renin-angiotensin-aldosterone system (RAAS) and the natriuretic-peptide system. While the over-activation of SNS is well documented in HF patients, beta-blockers (BB) represent one of the first-line HF treatment. The effects of BB are: reduction of heart rate and oxygen demand, beta-receptors modulation, reduction of RAAS activation, a protective effect by reducing catecholamine spill-over toxicity, anti-ischemic and anti-arrhythmic effects, antioxidant and antiinflammatory effects, improving myocardial protein synthesis and promoting peripheral vasodilation. The over-all effect of BB treatment leads to decreased morbi-mortality, decreased re-hospitalization and improvement of clinical symptoms in patients with HF. But not all BB have all these beneficial effects, so we need to emphasize that these effects are not a class effects. Only 3 BB have evidence of decreasing mortality in HF patients: bisoprolol, succinate-metoprolol, carvedilol, while nebivolol did not decrease mortality in elderly patients, but only CV death and re-hospitalization rate. A major step in the pharmacological treatment of patients with HF was represented by RAAS blockage with angiotensin converting enzyme inhibitors (ACEIs) which brought a reduction in mortality by 20-25%, decreased the number of rehospitalizations by 30-35%, prevent LV remodeling, decrease LV pre and afterload, stabilizes atherosclerotic plaques reducing the risk of ACS, have renoprotective effects (preventing renal failure and proteinuria) and decreases the risk of DM on-set. The RAAS blockade by of angiotensin receptor blockers (ARBs) have limited evidence compared to ACEIs, being recommended to be used only as an alternative to ACEIs- intolerant patients. That is why current guidelines recommend BB+ ACEIs (or ARBs to ACEIs intolerant patients) as the core-stone of pharmacological treatment in HF patients. However, in HF patients receiving BB+ ACEIs/ ARBs, re-hospitalization rate at 3 months is 30% and 5-year death-rate is 50%. In HF patients aldosterone levels are increased by 20 times, since there is an independent ATII production from the

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endothelial cells and smooth-muscle cells of blood vessels and heart. That is why is use of mineralocorticoid-receptor blockers antagonists (MRAs) have antifibrotic effect and cardiac and vascular level, decrease miocytes hypertrophy and apoptosis, decrease inflammation and calcifications and also decrease Na and water retention, K and Mg excretion. In RALES and EMPHASIS trails, the use of MRAs spiroloactone has proved reduction of morbi-mortality in patients with severe HF. If HF patients remain symptomatic after up-titration to maximum tolerate evidence-base dose of BB+ ACEIs/ ARBs, the current guideline recommend to add an MRA that up be up-titrated also to to maximum tolerate evidence-base dose. If the patients is still symptomatic and able to tolerate ACEIs (or ARBs) than the guideline recomend to replace ACEIs (or ARBs) with angiotensin-receptor neprilisin inhibitor (ARNI). The natriuretic-peptide system includes 3 structurally simmlar peptides which exerts protective cardio-renal effects (atrial natriuretic peptide (ANP), B-type natriuretic peptide and C-type natriuretic peptide), which practically antagonizes the effects of RAAS over-activation. The inactivation of the natriuretic peptides is accomplished by hydrolysis under the action of neprilisin, a reactive endopeptidase which is responsible for inactivation of several endogenous vasoactive peptides. Thus, the use of a neprilisin-inhibitor in patients with heart failure is obvious: increasing circulating levels of mature natriuretic peptides capable of exerting hemodynamic, natriuretic and diuretic effects. This combination - ARNI: dual inhibitor of angiotensin type 1 receptor and neprilisine (LCZ696: valsartan+sacubitril, 400 mg / day) was recently tested in comparison with ACEIs (enalapril 20 mg/day) in PARADGM-HF trail. After a median follow-up period of 27 months, the study was prematurely stopped due to the overwhelming superiority of LCZ696 treatment to enalapril, reducing the primary endpoint (risk of cardiovascular death with a risk of respiratory failure) by 20% and a total mortality of 16%. Other pharmacological options for patients with HF with reduced EF which remains symptomatic despite treatment with evidence-base dose of BB, ACEIs (or ARBs) and MRAs are represented by:

- Ivabradine – recommended if patients are in sinus rhythm with a HR>70bpm
- Hidralasine and isosorbid dinitrat – recommended as alternative to ACEIs/ ARBs if neither is tolerated, or if the patient remains symptomatic despite treatment BB, ACEIs (or ARBs) and MRAs
- Digoxin – recommended if patients associated atrial fibrillation of flutter with increased ventricular response, or if the patient is in synus rhythm bur intolerant to BB, or remains symptomatic despite treatment BB, ACEIs (or ARBs) and MRAs
- Nutritional supply by Q10-coenzyme, B1 vitamin, carnitine and taurine.

The diuretic treatment in patients with HF is only recommended for congestive symptoms relieve and maintain euvoolemia. While the pharmacological arsenal of HF with reduced LVEF is nowadays vast, in patients with HF with preserved or mid-range LVEF no treatment has proved reduction in mortality or morbidity. IN this patients diuretic treatment is recommended for symptom relieve, treatment of associated co-morbidities (HT, CAD, AF, etc). In conclusion, the pharmacological treatment available today has improved the morbi-mortality and functional capacity of HF patients, but due to its inherent limits, a significant proportion of patients remain symptomatic with frequent re-hospitalizations, an limited functional capacity and still a high mortality rate.

## Biography

Maria Dorobantu has worked as senior specialist in internal medicine and Senior specialist in cardiology during 1990-1996. She is Director of the Research Center of Excellency for the diagnosis and treatment of cardiovascular emergencies and she is Director of Hypertension Center of Excellence, European Society of Hypertension. She is Initiator and Coordinator for National Studys SEPHEAR (I-III). She is reviewer for multiple journals viz., American Heart Journal, Cor et Vasa, Journal of Hypertension, PLOS ONE.