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Safety and immunomodulatory action of epicardial patches combined with allogeneic adipose-derived mesenchymal stem cells in a rodent and porcine model of myocardial infarction

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The long-term benefit of epicardial collagen scaffolds seeded with autologous adipose derived-mesenchymal stem cells (Cg-ADSC) has been previously shown in rat and pig models of chronic myocardial infarction (MI). In contrast to direct intramyocardial administration of ADSC, epicardial delivery using collagen scaffolds enhanced stem cell engraftment and improved cardiac function, which was mediated through a decrease on myocardial remodeling and an increased vasculogenesis. In order to get into the clinical scenario, collagen scaffolds were seeded with allogeneic ADSC and manufactured under GMP standards. Their safety was confirmed under GLP conditions in different rodent models of tumorigenicity, biodistribution and toxicity and their putative immunogenic action analyzed in a pig chronic MI model. All the animal studies were performed according to the principles of laboratory animal care. Thus, tumorigenicity was evaluated in Rag2-/- immunodeficient mice subcutaneously implanted with the cellularized patch. No tumoral or differentiated cells were detected after 3 and 8 months of implantation (n=10/group). Also, ADSC distribution was shown to be confined to the cardiac tissue when implanted in the infarcted rat hearts. Cells were no detected in reproductive organs or brain (among other organs) 7 or 30 days post-implant (n=5/group). Importantly also, toxicity studies showed no adverse effects 2, 10, 30 and 90 days post-implantation in infarcted and healthy Nude rats (n=6/group). Clinical biochemistry, hematological and coagulation blood parameters together with urine analysis did not show significant changes. Necropsy and anatomopathological analysis did not reveal significant alterations due to the patch, neither.

Next, the inflammatory and immune response towards the allogeneic patch was analyzed in chronically infarcted pigs implanted with 50 million ADSC injected or implanted in combination with the collagen scaffold. Untreated infarcted animals were included as control group (n=8/group). The immune response was analyzed before implantation and 15, 30 and 90 days post-implant, determining the evolution of lymphocyte populations, monocytes, granulocytes and leukocytes in blood as well as levels of immunoglobulins and serum proteins. No significant changes were globally detected in any of the parameters analyzed. Moreover, blood biochemical parameters indicated a well preserved hepatic and renal function in all groups through the study.

In conclusion, treatment of the heart with an allogeneic Cg-ADSC patch is a safe treatment and do not induce an adverse inflammatory reaction, which could be a promising therapy for the treatment of ischemic patients.

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The long-lasting symptomatic benefit induced by lung ultrasound-guided therapeutic thoracentesis in refractory congestive heart failure: a retrospective cohort study

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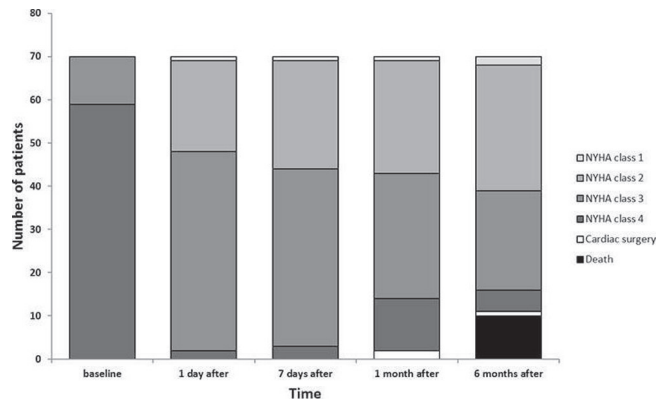
Background: Pleural effusion refractory to diuretic treatment is frequent in advanced congestive heart failure (HF). Therapeutic thoracentesis (TT) is a time-honored practice, recently made simpler and safer by guidance with lung ultrasound (LUS).

Purpose: To assess the feasibility and clinical impact of LUS-driven TT in refractory HF.

Methods: In a retrospective analysis of a single center 10 years (2007–2017) experience, we recruited 373 patients (180 females, age 69.5±12.4 yrs) with: 1. HF with reduced ejection fraction (26±12%, by 2D echo, modified biplane Simpson method); 2. NYHA class ≥3; 3. Maximal tolerated medical therapy (mean furosemide dose 191±173 mg); 4. Pleural effusion ≥ moderate at LUS, with maximal interpleural space >20 mm (sitting position, subscapular to midaxillary line). The underlying cause of HF was post-ischemic (32.9%) or idiopathic (41.4%) cardiomyopathy, severe aortic stenosis-regurgitation (14.3%), severe mitral regurgitation-stenosis (11.1%) and repaired congenital defect (0.3%). NT-BNP (available in 14 patients) was 12,717±4,575 pg/mL at study entry. All patients underwent LUS-guided therapeutic thoracentesis (TT). Medium-term follow-up information was available in 70 patients. Nineteen patients also underwent six-minute walk test (6MWT) before and after TT.

Results: LUS-guided TT was feasible and uneventful (462 procedures, 392 of them right-sided) in all patients. Evacuated pleural fluid by passive drainage was 1030±534 mL (range 200 to 2500). The maximal interpleural space was

73.6±15.6 mm before and 12.4±3.1 mm after TT (p<0.001). TT induced an immediate symptomatic improvement in all patients, with NYHA class decrease from 3.84±0.37 pre- to 2.7±0.55 post-TT (P<0.001). The improvement was short-lived (few hours) in 11%, and long-lasting (for weeks and months) in 89% of patients, in spite of largely unchanged medications (see figure). The 6MWT was 52±29 m before, 117±37 m at 2 hours after, 146±45 m one day after, 262±45 m one week after and 287±56 m one month after TT (p<.001 for all inter-group differences).



NYHA class during time

Conclusion: This single-center, retrospective study demonstrated the efficacy of LUS-driven TT of pleural effusion in decompensated HF patients. TT induces immediate, often dramatic, symptomatic relief usually accompanied by persistent improvement.

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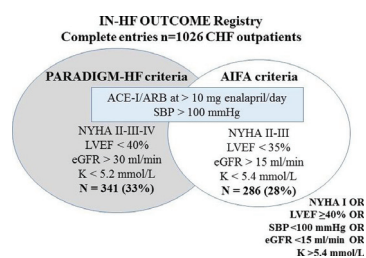
Real world eligibility and prognostic relevance for sacubitril/valsartan in unselected heart failure outpatients: data from an Italian registry (IN-HF outcome)

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Background: Although Angiotensin-Receptor-Neprilysin Inhibitors (ARNI) are recommended by all international guidelines for outpatients with chronic heart failure (CHF) and reduced ejection fraction (EF) who remain symptomatic despite optimal conventional drug treatment, uptake of this proven beneficial therapy in clinical practice takes time. In Italy ARNI are reimbursed by the National Health Service since March 2017 within criteria set by the national Medicines Agency (AIFA) mandating patient inclusion in a dedicated AIFA monitoring registry (AIFA-MR).

Aim and methods: We aimed to assess the eligibility profile for ARNI treatment of CHF patients who had been enrolled in a nation-wide all comers HF outpatient Italian Registry according to the drug's indication criteria from PARADIGM-HF and AIFA-MR, respectively. Discrepancy of inclusion thresholds for NYHA class, LVEF, eGFR and potassium between AIFA-MR and PARADIGM-HF criteria are reported in the figure.

Results: Among 1026 patients enrolled in the registry, ARNI-eligible subjects differed from ineligible ones for younger age, lower proportion of women (16%, p=.003, and 18%, p=.012, vs 25%), and higher proportion implanted an ICD (34%, p<.0001, and 26%, p=.0006, vs 17%) by both AIFA-MR and PARADIGM-HF criteria. ARNI-eligible and ineligible patients by PARADIGM-HF criteria had



similar 1-year CV mortality (2.9% vs 4.7%, $p=.19$) and 1-year all-cause (27% vs 24%, $p=.39$) and CV hospitalization rates (20% vs 18%, $p=.48$). Conversely by AIFA-MR criteria ARNI-eligible patients had significantly higher 1-year CV mortality (6.3% vs 3.2%, $p=.03$) and 1-year all-cause (32% vs 22%, $p=.001$) and CV admission rates (28% vs 16%, $p<.0001$) than ineligible subjects.

Conclusions: Up to one third of CHF outpatients enrolled in a large cardiology registry were eligible for ARNI. Enlarging eligibility criteria to allow treatment of CHF patients with worse renal function and setting LVEF threshold to $<35\%$, selects a subgroup with higher 1-year CV mortality and hospitalization rates. Provided that tolerability is confirmed, AIFA-MR criteria may identify patients with higher event rates at one year, who could particularly benefit from ARNI and may enhance treatment cost-effectiveness.

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Adherence to lifestyle therapy in patient with chronic heart failure and comorbidity

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Introduction: Low adherence to treatment is a widely extended problem among patients with chronic heart failure (CHF). Besides medical treatment, lifestyle modifications improves quality of life and prognosis of patients with cardiovascular diseases. However, influence of comorbidity on adherence to lifestyle therapy in patients with CHF have not been studied yet.

The aim of this study was to investigate awareness and adherence to lifestyle therapy in patient with CHF and comorbidity.

Methods: 203 patients with CHF (130 males and 73 females, mean age was 62 ± 10 years) were studied. CHF was defined according to ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, 2016. The main causes of CHF were coronary heart disease and arterial hypertension. Charlson comorbidity index was calculated. Awareness of lifestyle modifications was determined using a questionnaire developed in our clinic and used in previous scientific studies. Adherence to lifestyle therapy was considered satisfactory when patients performed at least 80% of the recommendations. Quality of life was estimated using SF-36 Health Status Survey. Patients were followed up for 1 year.

Results: The awareness about lifestyle modifications in patients with CHF ranged from 38.9% (daily control of body weight) to 87.2% (reduced intake of dietary sodium). 33 (16.3%) patients had self-control diaries. Only half of the patients, who known about lifestyle modifications, performed medical recommendations. Adherence to lifestyle therapy was from 7.9% (daily weight control) to 37.9% (reduced intake of dietary sodium). The main types of physical activity in patients with CHF were walking - 49 (22.7%) and morning exercises - 31 (15.3%). Patients with CHF, engaging in physical activity, had higher rates quality of life according to the scales of the physical component of health: physical functioning ($r=0.30$, $p=0.003$) and physical-role functioning ($r=0.31$; $p=0.001$); and on the scale of the psychological component of health: emotional-role function ($r=0.30$, $p=0.002$). Only 37 (18.2%) patients were full adherence to lifestyle therapy. Age adjusted Charlson comorbidity index was 5.0 ± 2.1 scores. There were not differences in adherence to lifestyle therapy in patients with CHF, depending on the level of comorbidity.

Conclusions: Only every fifth patient with CHF was adherence to lifestyle therapy despite of the level of awareness about lifestyle modifications and comorbidity.

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Effect of flexible diuretics regimen on sudden weight changes

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Background: There is a homebased tool for patients with heart failure (HF), which monitors symptoms, titrates diuretics and educates the patient about living with HF. Weight is monitored daily, and controls a flexible diuretics regimen. If the weight is increased by >2 kg in 3 days or less, the dose is increased to a patient specific higher level, which is maintained for two days. If the weight then returns to baseline, the dose returns to the lower level, otherwise the patient is alerted and encouraged to contact his/her health care provider (HCP).

Purpose: Investigate how often the increased diuretics dose could reverse the weight increase.

Methods: The system automatically registers when the threshold for a weight increase event is exceeded, and also whether the subsequent dose increase returned the weight to the level before the onset of the rapid weight gain, with a tolerance of ± 0.6 kg.

Results: Data stored in 92 systems was analyzed and the systems had been actively used by patients for 6 months in different parts of Sweden. 33% of the patients were female and the mean age was 75. There was a total of 137 dose increases, spread out over 49 patients (53% of the patients) and on average there were 1.5 alerts per patient.

45% of the increased dose of diuretics managed to return the weight to within ± 0.6 kg of the weight prior to the sudden weight increase, and the remaining 55% resulted in an alert.

Conclusions: In 45% of the cases where a potentially deleterious rapid weight gain occurred, the flexible diuretics regimen implemented in the tool successfully returned the weight back to the baseline level. This suggests that adherence to

a flexible diuretics regimen should be encouraged, as it may ease suffering and save health care resources.

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Effects of exercise training on cardiovascular autonomic modulation and skeletal muscle tissue in chagasic cardiopathy patients and preserved systolic function

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Background: The benefits of aerobic exercise training (ET) in cardiovascular autonomic control and skeletal muscle of heart failure patients are well established. The study hypothesis was that ET improves cardiovascular autonomic function and structure, and muscle metabolism in chronic chagasic cardiopathy (CCC) patients even though they have preserved systolic function, considering that some of these patients develop the dilated form with ventricular dysfunction and its serious consequences.

Purpose: To evaluate the effects of ET on cardiovascular autonomic control and skeletal muscle tissue in CCC patients and preserved systolic function.

Methods: Patients with two positive serological reactions for Chagas disease, electrocardiographic alterations, left ventricular ejection fraction $\geq 55\%$ and age between 30 and 60 years were included. Eight patients completed the ET protocol (ET, $n=08$) and ten patients completed clinical follow-up (NoET, $n=10$). Muscular sympathetic nerve activity (MSNA) was measured using microneurography technique and muscle blood flow (MBF) by the venous occlusion plethysmography technique. Cardiac baroreflex sensitivity was evaluated by infusion of vasoactive drugs. Functional capacity was determined by cardiopulmonary exercise test. Vastus lateralis muscle biopsy was performed for histological analysis of muscle fibers and for Atrogin-1 and MuRF-1 gene expression evaluation. The ET program consisted of three 60-minute exercise sessions per week for four months.

Results: Regarding ET markers, there was a reduction in resting heart rate (66.1 ± 2.6 vs 59.4 ± 3.3 beats/min; $p=0.003$) and an increase in peak oxygen consumption (24.4 ± 2.4 vs 28.1 ± 1.7 ml/kg/min; $p=0.03$). ET reduced the sympathetic hyperactivity, contributing to an increase in MBF. ET reduced MSNA (31.9 ± 3.8 vs 22.8 ± 2.6 burst/min; $p=0.008$), as well as cardiac (68 ± 4 vs 60 ± 4 nu; $p=0.004$) and vasomotor sympathetic activity (46 ± 5 vs 37 ± 3 nu; $p=0.04$), and improved cardiac baroreflex sensitivity (-0.23 ± 0.1 vs -0.46 ± 0.1 ; $p=0.04$ for increases in BP and -0.48 ± 0.1 vs -1.00 ± 0.3 ; $p=0.04$ for decreases in BP). A reduction of MSNA was associated to a reduction in cardiac ($r=0.67$; $p=0.013$) and vasomotor ($r=0.81$; $p=0.003$) hyperactivity, improved cardiac baroreflex sensitivity for increases ($r=0.72$; $p=0.20$) and decreases in BP ($r=-0.82$; $p=0.001$), and reduced Atrogin-1 ($r=0.86$; $p=0.02$) and MuRF-1 ($r=0.64$; $p=0.06$) gene expression. After the four-month period, the ET group presented lower Atrogin-1 gene expression than the NoET group (0.49 ± 0.2 vs 2.27 ± 0.4 u; $p=0.001$).

Conclusion: ET significantly improved autonomic dysfunction, MBF and functional capacity of CCC patients and preserved systolic function. In addition, reduced ANSM was associated with improved cardiac baroreflex sensitivity, reduced sympathetic cardiovascular tone, and reduced Atrogin-1 and MuRF-1 gene expression, which are involved in muscle atrophy.

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A new prognostic indicator in patients with acute decompensated heart failure including both ambulatory and nutritional statuses

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Background: Nutritional status as well as exercise capacity is related to the prognosis especially in elderly patients with heart failure.

Purpose: The purpose of this study was to explore a strong prognostic indicator in elderly patients with acute decompensated heart failure (ADHF) by including both ambulatory and nutritional statuses.

Methods: A total of 203 patients hospitalized with ADHF (mean age, 82 ± 10 years old) were enrolled. We evaluated the prognostic nutrition index (PNI) on hospital admission and discharge. PNI was calculated by $10 \times$ serum albumin (g/dl) + $0.005 \times$ total lymphocyte count (per mm^3) and $\text{PNI} \leq 38$ was considered as malnutrition. Ambulatory status was evaluated by a simple walking test during cardiac rehabilitation if a patient could walk 200 meters within Borg scale ≤ 13 without critical changes in vital signs. Clinical endpoints were the mortality and heart failure hospitalization within 2 years of discharge.

Results: Eighteen % of patients showed $\text{PNI} \leq 38$ on admission and 20% on discharge. $\text{PNI} \leq 38$ on discharge was more strongly related to the mortality [hazard ratio (HR) 3.84, 95% confidence interval (CI) 1.83–8.03, $p<0.0001$] than $\text{PNI} \leq 38$ on admission was (HR 2.30, 95% CI 1.07–4.93, $p=0.005$). Forty-five % of patients could not walk 200 meters, which was significantly related to the mortality [HR 4.34, 95% CI 2.47–7.65, $p<0.0001$]. However, neither malnutrition on discharge nor low ambulatory status was related to heart failure hospitalization (HR 1.10, $p=0.70$; HR 1.32, $p=0.14$, respectively). We divided patients into group G (both