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Original Article

From Emergency Department to clinic center: management of patients with Heart Failure with Reduced Ejection Fraction

Dal Pronto Soccorso al Reparto di degenza: gestione dei pazienti con scompenso cardiaco a FE ridotta

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ABSTRACT

Aims: primary outcomes - cardiovascular and all-cause mortality evaluation within 1 year in elderly patients enrolled with Angiotensin Receptor Inhibitor (ARNI) and/or Sodium Glucose Co-Transporter Type 2 Inhibitors (SGLT2-i) in an Internal Medicine Department; recurrent hospitalization assessment for acute Heart Failure with Reduced Ejection Fraction (HFrEF); length of hospitalization analysis compared to not-enrolled patients. Secondary endpoints - to identify any parameters predicting the length of hospitalization; safety assessment through the incidence of complications and treatment interruption.

Materials and Methods: prospective observational real-life cohort study that analyzes the recruitment during hospitalization and follow-up 3-6-12 months after discharge. Several clinical parameters were recorded for each patient of any ethnicity, considering a diagnosis of acute HFrEF with NT-proBNP and chest x-ray.

Results: the enrolled group (34 patients) showed a hospitalization period lower than the not-enrolled one. The re-hospitalizations percentage was inferior to Randomized Clinical Trials (RCTs) for ARNI. Cardiovascular-cause mortality, symptomatic hypotension, and Urinary Tract Infections (UTI) were lower than RCTs data. Age, eGFR, NT-proBNP, Cumulative Illness Rating Scale (CIRS), and severe comorbidities, except for EF, predicted the lengthening of hospitalization. Hypoglycemia wasn't recorded.

Conclusions: ARNI/SGLT2-i are effective and safe in elderly patients. Comorbidities and bio-humoral features influence HFrEF and quality of life. The future aim is to confirm the results obtained so far.

Obiettivi: endpoint primari - valutare la mortalità cardiovascolare e per tutte le cause nel primo anno in pazienti anziani arruolati con *Angiotensin Receptor Inhibitor* (ARNI) e/o *Sodium Glucose Co-Transporter Type 2 Inhibitors* (SGLT2-i) in un reparto internistico; valutare il ricovero ricorrente per *Heart Failure with Reduced Ejection Fraction* (HFrEF) acuto; analizzare la durata del ricovero confrontandola con i non arruolati. Endpoint secondari: identificare i parametri predittori della durata della ospedalizzazione; definire la sicurezza tramite l'incidenza di complicanze e di interruzione del trattamento.

Materiali e Metodi: studio *real-life* prospettico osservazionale di coorte che analizza l'arruolamento durante il ricovero ed il follow-up 3-16-12 mesi dopo la dimissione. Sono stati registrati molteplici parametri per ogni paziente di diversa etnia, valutando la diagnosi di HFrEF acuto con NT-proBNP e RX-torace.

Risultati: la durata del ricovero nel gruppo arruolato è stata inferiore rispetto ai non arruolati. La percentuale di re-ospedalizzazioni è stata inferiore rispetto a quella dei *Randomized Clinical Trials* (RCT) per ARNI. La mortalità cardiovascolare, l'ipotensione sintomatica e le Infezioni delle Vie Urinarie (IVU) sono state inferiori rispetto ai dati dei TCR. Età, eGFR, NT-proBNP, *Cumulative Illness Rating Scale* (CIRS), comorbidità severe, eccetto FE, sono stati predittori della durata del ricovero. Non sono state registrate ipoglicemie.

Conclusioni: ARNI/SGLT2-i sono efficaci e sicuri nei pazienti anziani. Comorbidità ed indici bioumorali influenzano la qualità di vita e la storia naturale di HFrEF. L'obiettivo futuro è la conferma dei risultati ottenuti sin qui.

Introduction

The standard of care for Heart Failure with Reduced Ejection Fraction (HFrEF) combines inhibition of the Renin-Angiotensin-Aldosterone System (RAAS) and blockade of the sympathetic system.[1] Evidence derived from previous large Randomized Clinical Trials (RCTs)[2] shows benefits in terms of mortality and fewer hospitalizations in patients treated with Angiotensin-Converting Enzyme Inhibitors (ACE-i), Beta-Blockers (BBs) and Mineralocorticoid Receptor Antagonists (MRA).[3] After approximately 15 years of absence of new therapeutic strategies, 2014 year marked the beginning of a "new era" in the treatment of HFrEF.[4] To date, five landmark randomized controlled trials have been published in less than six years, and four new drug classes have

expanded the catalog of possible treatments for HFrEF beyond conventional neuro-hormonal blockade.[5] These new drugs, namely neprilysin, Angiotensin Receptor Inhibitor (ARNI),[6] and Sodium Glucose Co-Transporter Type 2 Inhibitors (SGLT2-i), have been shown to further increase survival and prevent hospitalizations in patients with HFrEF.[7] The new 2021 ESC Guidelines[8] have therefore implemented the evidence-based recommendations compared to the latest 2016 Guidelines, in particular for the treatment of patients with HFrEF.[9] However, the data available so far are less strong on HFmrEF and HFpEF (Heart Failure With Preserved Ejection Fraction).[10] Nevertheless, the serial clinical reassessment process, in particular immediately after discharge in patients hospitalized for HF, hasn't yet been defined as a whole; at the same time, there is a lack of real-life data on a specific population of multi-pathological and elderly patients, such as those often belonging to Internal Medicine Units.[11] Therefore we present below a registry that can provide further elements to the clinician to make the most of all the new pharmacological strategies for HFrEF in clinical practice,[12] in the context of newly hospitalized frail patients with multiple comorbidities. Further data in this area are, however, highly desirable: studies carried out on a wider population would allow for a deeper understanding of the critical issues for targeted screening and follow-up interventions to prevent disease flare-ups or intercept them in the earliest stages in order to carry out adequate treatments that reduce hospitalizations and death.

Materials and Methods

This study aims to collect data on the clinical history of patients suffering from HF, as defined by the 2021 ESC Guidelines, who are treated chronically with specific drugs and with new therapeutic strategies (SGLT2-i and ARNI). Consecutive patients admitted to the 2nd Medicine Department of the Busto Arsizio Hospital, ASST Valle Olona, Lombardy, Italy, from January to October 2022 were recruited. The registry is designed for observational purposes only and isn't intended to have any influence on the treatment of individual patients included. Patients are enrolled at the time of prescription of ARNI or SGLT2-i. The general objectives of the study are to provide a better evaluation of the efficacy and safety of different treatment options,[13] in a particular population of multi-pathological patients rarely considered in clinical trials, and to improve our understanding of the risk/benefit ratio of various drugs. The registry is open to the participation of clinical centers and individual specialists who deal with the management of patients with HF.[14]

Outcomes

The primary endpoints were: i) to evaluate cardiovascular-cause and all-cause mortality within 1 year of the event in elderly patients hospitalized in an Internal Medicine Department and enrolled with ARNI and/or SGLT2-I;[15] ii) to assess recurrent hospitalization for acute HFrEF within 1 year of the event in the same cohort;[16] iii) finally, to evaluate the length of hospital stay compared to patients who can't be enrolled with ARNI and/or SGLT2-I.[17]

The secondary endpoints were: i) to identify any parameters predicting the length of hospital stay in patients with HFrEF;[18] ii) to evaluate the ARNI and SGLT2-i safety profile in elderly patients, by analyzing the incidence of complications and the percentage of treatment interruption.[19]

Study design

This is a prospective observational real-life cohort study that consists of two parts: the real recruitment, with follow-up during hospitalization in order to confirm or not the indication for ARNI or SGLT2-I at the admission, then telephone or outpatient follow-up 3, 6, and 12 months after discharge to record any suspension of drugs, possible complications, side effects, new hospitalizations for decompensation cardiac or other clinical reasons (in particular urinary tract infections), possible death due to HF or other causes.[20] Consecutive patients admitted to the 2nd Medicine Department of the Busto Arsizio Hospital, ASST Valle Olona, with a confirmed diagnosis of acute HFrEF, from January to October 2022 were recruited. Patients discharged in September 2022 were also re-evaluated 1 month later. They were identified by direct medical record review or search in the hospital database, using the discharge codes according to the ICD-9-CM.[21]

Study patients

At the time of enrollment, demographic and anthropometric features were recorded for each patient, *i.e.* age, sex, eventual obesity, main comorbidities by noting the score on the Cumulative Illness Rating Scale (CIRS), renal function and clearance according to the Cockroft-Gault formula, NT-proBNP value, NYHA class, days of hospitalization, therapies in progress for HF and presence of oral hypoglycemic drugs, need for home care.[22] The EF was recorded through analysis of the available clinical documentation (within the previous 6 months), the Emergency Room report if including a cardiological examination, or in the absence of them, through a specific specialist examination or ultrasound performed in the department.[23] Further clinical parameters not recorded in the definitive database but considered in order to define the indication for recruitment were: vital parameters at baseline (*i.e.* within 48 hours of hospital admission), any oxygen requirement, blood gas items including lactate level, blood tests at baseline (also to exclude concomitant infectious causes),[24] glycemic profile, any significant Electrocardiogram (ECG) alterations (branch blocks, A-V blocks, presence of arrhythmias) or significant valvular diseases.[25] Recruitment was preceded by written consent to personal data treatment and participation of each enrolled patient, including adequate information about the objectives, risks, and benefits related to the study itself and the need for follow-up. This study was submitted to the local Ethics Committee, and it was conducted, evaluated, and documented according to the ethical principles set out in the Declaration of Helsinki, 2008 6th revision, and the guidelines on good clinical practice of the European Community, as maximum individual protection. All patient names were shared only among study participants. They were numbered consecutively according to the chronological order of enrollment; the number assigned to each patient during the study uniquely identified a specific person through available documentation (including medical record number and date of birth). Each researcher kept a personal copy of the database in order to retrieve the information at the time of the statistical analysis.

Study procedures

Each hospitalized patient suffering from HFrEF was evaluated upon admission and during hospitalization to start SGLT2-i and/or ARNI, specifically to evaluate their prescription criteria based on the anamnesis and clinical examination by reporting the main impediments, such as hyperkalemia, recurrent urinary tract infections,

acute or chronic renal failure, hypotension or severe hypoglycemia, severe prognosis *quoad valetudinem* or *quoad vitam*.

Adult male and female patients of any ethnicity were included.[26]

The patient inclusion criteria were: i) adult patients who have signed a written consent; ii) acute HFrEF clinically diagnosed, with NT-proBNP values higher than the reference ranges for hospitalized patients (>300 pg/ml), chest x-ray indicative of small circulation congestion and/or pleural effusion, increase in cardio-thoracic index;[27] iii) hemodynamic stability at the time of HFrEF diagnosis.[28]

The patient exclusion criteria were: i) patients under the age of 18; ii) patients with HFmrEF or HFpEF;[29] iii) mentally incapacitated patients.

Statistical analysis

The data was collected from the study participants and entered into a specific MS Office Excel file.

Regarding the primary endpoint, the categorical variables evaluated in the study were expressed as a numerical value and/or as a percentage. Continuous variables were reported as means (±Standard Deviation, SD) or medians (±Interquartile Range, IQR), depending on the normal distribution of the data. The differences, when the sample size allowed it, were analyzed using chi-square tests, t-tests, or Mann-Whitney U-tests, as appropriate;

Regarding secondary endpoints, the categorical variables evaluated in the study were expressed as a numerical value and/or as a percentage. Continuous variables were reported as means (±Standard Deviation, SD) or medians (±Interquartile Range, IQR), depending on the normal distribution of the data. To identify any predictors of reduction in hospital length of stay, Hazard Ratios (HR) and their 95% Confidence Intervals (CI) were estimated using univariate and multivariable Cox regression analysis.

Results

A total of 82 patients were assessed as eligible, including 47 males and 35 females. There were 34 patients enrolled, corresponding to 41.5% of the total, of which 18 were males and 16 were females. Six patients were enrolled only with ARNI, 20 were enrolled only with SGLT2-i, and 8 were prescribed the ARNI/SGLT2-i combination. Thus, 14 were enrolled with ARNI, and 28 were enrolled with SGLT2; of them, 17 were prescribed empagliflozin, and 11 were prescribed dapagliflozin.

Considering the features of the global population and the subpopulations, several interesting data were recorded. Compared to the populations of the main studies (Emperor-reduced and Paragon-HF), our patients showed significantly higher values of NT-proBNP, worse values of renal function, higher mean age, and comparable EF. Furthermore, a greater percentage was in NYHA class III. The main comorbidities of those who discontinued, were re-hospitalized, or died in follow-up were the most serious in prognostic terms: type 2 diabetes mellitus, previous circulatory arrest, chronic peripheral obliterating arterial disease, previous stroke, dementia, Parkinson's disease.

Similarly, patients who showed complications during follow-up had a greater need for home care than the whole enrolled and those without complications (83.3% *vs* 70.6% and 79.2%, respectively). Patients who suspended one or both drugs during follow-up, were re-hospitalized, or died were 12/34 (35.3%). The data for each of the three subgroups is analyzed below in the outcomes sections (*Supplementary Figures 1-10*).

Primary outcomes

Efficacy

Regarding the length of hospital stay, the whole enrolled group showed a hospitalization period of 8.8 days, the not-enrolled group 9.3 days, and those complicated in follow-up 9.7 days.

Analyzing re-hospitalizations for HF, this occurred in 7/34 patients (20.6%), of which 5/34 (14.7%) were for recurrent HF. There were 3 re-entries at 3 months and 2 re-entries at 6 months, *i.e.* 7.1% in ARNI and 17.9% in SGLT2-i, while the Paradigm-HF trial registered 12.8% and the Emperor-Reduced trial reported 13.2%.

Regarding mortality from HF, all-cause mortality occurred in 5/34 patients (14.7%), of which 2/34 (5.9%) due to recurrent HF; cardiovascular-cause mortality was registered twice: both patients were enrolled only with SGLT2-i (7.1%), with worse parameters than the complicated subgroup in follow-up (*i.e.* renal function). The Paradigm-HF registered 13.3% mortality, the Emperor-Reduced 10%; therefore, the effectiveness of ARNI and SGLT2-i is shown even in severe polypathological patients.

Secondary outcomes

As regards parameters predicting the length of hospital stay, we registered age >80 years, eGFR ≤30 ml/min acc. Cockroft-Gault, NT-proBNP on admission >10,000 pg/ml, CIRS score >20, personal history of cancer or dementia, while EF doesn't appear to be related to the lengthening of hospitalization (8.5 days if EF ≤30%, 9 days if EF >30%).

Safety

Considering the patients who underwent interruption of treatment with one or more drugs during follow-up, they were overall 9/34 (26.5%), of which 7/28 (25%) enrolled with SGLT2-i and 2/14 (14.3%) enrolled with ARNI.

Regarding the incidence of complications, symptomatic hypotension for ARNI was recorded in 2 women (14.3%) with EF 25% and 20%, respectively. The first one had already had the drug suspended in the past due to hypotension, the second one hadn't been prescribed it due to the high risk of hypotension and falls.

Severe acute kidney injury, volume depletion, and hyperkalemia occurred in 17.9% of SGLT2-i enrollees; the literature reports a 9.5% incidence, but not serious enough to cause its suspension. However, considering the characteristics of the population (eGFR 39 *vs* 61 ml/min), a minimal worsening of renal function may be enough to make patients no longer eligible.

Discussion

Regarding enrollment, 35 patients were excluded due to severe prognosis at entry, with life expectancy probably less than a year, or evident poor adherence to therapy and follow-up, for example, severe cognitive deterioration or inadequate home setting. Twenty were excluded due to failure to update the AIFA therapeutic plan on HFrEF in the absence of diabetes (until May 2022).

About the efficacy features, the duration of the index hospitalization influences the risk of re-hospitalization in the short term. Specifically, the greater risk is confirmed in patients with longer hospital stays compared to the same objectives required by the regional directives. Moreover, these data reveal the efficacy of ARNI even for elevated natriuretic peptide values, severely

reduced EF, or impaired renal function. At the same time, there may have been an excessive reduction of diuretics after the prescription of gliflozine, or these data may reveal a reduction of the nephro-protective effect of SGLT2-i for very compromised renal function values.

Analyzing the secondary outcomes, the parameters that we considered are directly related to the clinical and management complexity of the patient, influencing discharge choices, *e.g., due to the need to improve home care or start an institutionalization process, with inevitable lengthening of the* hospitalization period. Moreover, modern therapeutic solutions allow an excellent outcome even in patients with severe HFrEF. Besides regarding the safety features, our results could be considered in line with the literature data for sacubitril-valsartan (hypotension 17.6%), considering the extremely fragile patients with a prior risk of hypotensive events. On the other side, UTI or complicated genital infections are inevitably more prevalent among polypathological patients. They occurred in 3.6% *vs* 5.3% in the literature, also considering uncomplicated infections. A single prescription had been attempted in a complex patient suffering from obesity and diabetes, with poor compliance and high basal risk of relapses. Severe hypoglycemia has never been recorded in line with RCTs, confirming the protective effect with a low risk of progression toward insulin dependence.

Limitations of the study

The main flaws of our study are the single center setting since the study was intended to obtain preliminary data, the relatively low sample size for statistical analysis, the lack of strong data from previous research studies on the topic, the observational design, and the time constraints.

Conclusions

The study confirms the complexity of the clinical panel for HF, particularly in internal medicine patients: clinical management should, therefore, be improved by considering a multidisciplinary diagnostic-therapeutic approach.

These two classes of drugs are effective and safe, and the personalization of therapeutic choices is significant. Furthermore, the positive impact on quality of life is of considerable interest, as in the future, our healthcare systems will increasingly have to deal with the raised prevalence of elderly patients, whose increased life expectancy hasn't been concurrently associated with an improvement in quality of life so far.

The results showed that the reduction of the diuretic dosage should probably be limited and based on the clinical response after starting gliflozine; otherwise, there's an increased risk of re-hospitalization. It's crucial to implement outpatient follow-up and schedule a first check-up examination within a few days after discharge.

Comorbidities and basal bio-humoral features play an important role in influencing both the underlying disease and the quality of life: the main future aim, to be pursued through further studies, will be the confirmation of the results obtained so far through a hopefully multi-center trial.

Finally, as the prevalence of HFrEF will tend to decrease in the future with a simultaneous increase of HFpEF, reasonably, the next guidelines will provide new and specific indications for this category of HF.

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Ethics approval and consent to participate: this study was submitted to the local Ethics Committee and it was conducted, evaluated and documented according to the ethical principles set out in the Declaration of Helsinki, 2008 6th revision, and the guidelines on good clinical practice of the European Community, as maximum individual protection. All patient names were shared only among study participants.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

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Online: supplementary material

Supplementary Figure 1. Angiotensin Receptor Neprilysin Inhibitor (ARNI) and Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2-i) distribution in the global population. Values are expressed as absolute numbers and percentages (%).

Supplementary Figure 2. Clinical features of the global population and of the subgroups (enrolled, not enrolled, and complicated patients during follow-up, that is, those who discontinued, were re-hospitalized, or died in follow-up). Continuous variables are reported as means (± Standard Deviation, SD). CIRS, Cumulative Illness Rating Scale; EF, Ejection Fraction; eGFR, Estimated Glomerular Filtration Rate; NYHA, New York Heart Association Classification.

Supplementary Figure 3. Main comorbidities in the global population and in the subgroups. Those who discontinued were re-hospitalized, or died in follow-up had the most serious comorbidities in prognostic terms. COPD, Chronic Obstructive Pulmonary Disease; AF, Atrial Fibrillation; AOCP, Chronic Obstructive Obliterative Arteriopathy; DM2, Type-2 Diabetes Mellitus.

Supplementary Figure 4. Length of the hospital stay. The whole enrolled group showed a hospitalization period of 8.8 days, the not-enrolled group 9.3 days, and those complicated in follow-up 9.7 days.

Supplementary Figure 5. Re-hospitalizations for Heart Failure (HF) occurred in 7/34 patients (20.6%), of which 5/34 (14.7%) were for recurrent HF. There were 3 re-entries at 3 months and 2 re-entries at 6 months, i.e., 7.1% in Angiotensin Receptor Inhibitor (ARNI) and 17.9% in Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i), while the Paradigm-HF trial registered 12.8%, and the Emperor-Reduced trial reported 13.2%.

Supplementary Figure 6. Mortality due to Heart Failure (HF). All-cause mortality occurred in 5/34 patients (14.7%), of which 2/34 (5.9%) due to recurrent HF; cardiovascular-cause mortality was registered twice: both patients were enrolled only with Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i) (7.1%). The Paradigm-HF registered 13.3% mortality, the Emperor-Reduced 10%.

Supplementary Figure 7. Parameters predicting the length of hospital stay. Age >80 years, eGFR ≤30 ml/min acc. Cockroft-Gault, NT-proBNP on admission >10,000 pg/ml, CIRS score >20, personal history of cancer or dementia were confirmed as significant features, while EF didn't appear to be related to the lengthening of hospitalization (8.5 days if EF ≤30%, 9 days if EF >30%).

Supplementary Figure 8. Patients who interrupted treatment with one or more drugs during follow-up. Overall, 9/34 (26.5%) were enrolled with Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i), 7/28 (25%) with Angiotensin Receptor Inhibitor (ARNI), and 2/14 (14.3%) with ARNI. HF, Heart Failure.

Supplementary Figure 9. Incidence of complications (part 1). Symptomatic hypotension for Angiotensin Receptor Inhibitor (ARNI) was recorded in 2 women (14.3%). Literature data for sacubitril-valsartan showed hypotension in 17.6% of patients. See the text for further details. HF, Heart Failure.

Supplementary Figure 10. Incidence of complications (part 2). Severe acute kidney injury, volume depletion, and hyperkalemia occurred in 17.9% of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i) enrollees; the literature reports a 9.5% incidence. Urinary Tract Infections (UTI) or complicated genital infections occurred in 3.6% vs 5.3% in the literature, which also considers uncomplicated infections. Severe hypoglycemia has never been recorded in line with Randomized Clinical Trials (RCTs). See the text for further details. AKI, Acute Kidney Injury.