"CAROL DAVILA"
UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST
DOCTORAL SCHOOL
MEDICINE FIELD

Inflammation in chronic heart failure in relationship with standard applied treatment versus new pharmacological classes

PHD THESIS ABSTRACT

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2025

Content

List of abbreviations and symbols

ACE-I –angiotensin I converting enzyme inhibitors

AHA/ACC – American Heart Association/American College of Cardiology

AMI – acute myocardial infarction

ARB – angiotensin II receptor blockers

ARNI – angiotensin II receptor blockers and neprilysin inhibitors

BB – beta-blockers

CHF – chronic heart failure

CRP –C reactive protein

ESC – European Society of Cardiology

ESR – erythrocyte sedimentation rate

HFmrEF – heart failure with mildly reduced ejection fraction

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HF – heart failure

hsCRP – hypersensitive C reactive protein

IVC – inferior vena cava

IL – interleukin (1, 6, 8, 18, 33)

iNOS – inducible nitric oxide synthetase

LVEF – left ventricle ejection fraction

MPO – myeloperoxidase

MRA – mineralocorticoid antagonists

NO – Nitric oxide

RAAS – renin angiotensin aldosterone system

SGLT2i – sodium-glucose cotransporter 2 inhibitors

SNS – sympathetic nervous system

TNF alpha – tumor necrosis factor alpha

LV – left ventricle

The theoretical essence

This doctoral thesis started from the desire to study an extremely prevalent pathology worldwide, that provokes the entire medical community for centuries, but for which the last years have brought to the therapeutic arsenal new highly effective drug classes, that have mechanisms of action that are not fully understood yet.

Inflammation is the body's response to multifactorial aggression, representing the immune system's physiological defense mechanism. The intensity of this chain reaction involves multiple components with adverse effects on various devices, systems and organs. Chronic diseases with progressive evolution, with various localizations activate the immune system with the persistence of the inflammatory response and thus with local and systemic complications.

In the case of heart failure, chronic inflammation is the main pawn, which through cellular and biohumoral mechanisms, produces oxidative stress with systolic and diastolic cardiac dysfunction. A great amount of clinical and laboratory evidences has highlighted biologically active molecules that have deleterious cardiac and circulatory effects through a multitude of mechanisms and systems that produce cardiac remodelling, a theory which is called the neurohormonal model (1). This process includes the sympathetic nervous system (SNS), which is excessively activated (2) and the renin-angiotensin-aldosterone system (RAAS) which enters in action later. By stimulating AT1 (angiotensin 1) receptors, which cause vasoconstriction, stress, hyperproliferation and release of catecholamines, and inhibiting AT2 (angiotensin 2) receptors, which cause vasodilatation and anti-inflammatory effect, ventricular stiffening and remodelling are finally induced (3).

There are studies that show a correlation between proinflammatory markers' seric levels and cardiovascular events (4). In HFpEF, the proinflammatory marker levels elevation is caused by comorbidities, with nitroso-redox balance disturbance (5). In HFrEF, the incriminating element is myocardial injury, with synthesis of proinflammatory cytokines.

Among the main proinflammatory cytokines involved in the pathophysiology of CHF are TNF alpha (tumor necrosis factor alpha), IL-1 (interleukin 1), IL-6 (interleukin 6), IL-8 (interleukin 8), IL-18 (interleukin 18) , IL-33 (interleukin 33) (6–12).

C-reactive protein (CRP) is the most studied acute-phase reactant protein, which participates in the control of ischemia, in the myocardial tissue injury through complement activation (13).

CRP is an independent cardiovascular risk factor, being associated with increased cardiovascular events and cardiovascular mortality. CRP values >12 mg/L are associated with a high risk of mortality or readmission for decompensation within 3 months (14). A value > 3,23 mg/L is correlated with severe CHF, HFrEF and increased prevalence of atrial fibrillation (15).

Decompensations cause overstimulation of the immune system and over time, severe deterioration of cardiac function. Multiple clinical studies which contributed to the development of treatment and diagnostic guidelines, with periodic updates, led to the recent classifications, individualizing heart failure (HF) into 3 categories: heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF). In CHF there is an increased production of oxygen free radicals, with major inflammatory response and destructive effect (16).

The prognosis of CHF has improved considerably in recent years with new therapeutic classes, in terms of symptom control and mortality, as shown by randomized clinical trials (17). Classical anti-remodeling medication inlcudes: BB (beta-blockers), ACE-I (angiotensin I converting enzyme inhibitors) / ARB (angiotensină II receptor blockers) and MRA (mineralocorticoid antagonists) demonstrated a significant reduction in mortality and readmission rate in HFrEF cases. In HFpEF patients, they failed in achieving similar results.

New classes studied in patients with CHF (chronic heart failure): ARNIs (angiotensin II receptor blockers and neprilysin inhibitors) and SGLT2i (sodium-glucose cotransporter type 2 inhibitors) which have been the subject of many randomized clinical trials have proven their effect in HFrEF, by reducing the risk of mortality or readmission for CHF decompensation. Of these new classes, SGLT2i have shown similar effects in HFpEF, that is why they represent the first class of drugs with an anti-remodeling effect included in the ESC (European Society of Cardiology) guideline for HFpEF (indication I, level of evidence A). In HFrEF, the ESC guideline shows indication I, level of evidence A for: BB, ACE-I/ARB, MRA, SGLT2i and indication I, level of evidence B for ARNI.

The cardiovascular protective effects of these classes of anti-remodeling drugs are generated by several mechanisms, some of which have been demonstrated, others only postulated and still in research. The present doctoral study aims to evaluate the degree of systemic inflammation in CHF patients and how is influenced by the respective drug therapies.

The major hypothesis is that the intensity of inflammation is greater as cardiac dysfunction is more severe. In this way the markers of inflammation correlate directly proportional with markers of heart failure, and under the effect of new drug classes, markers of inflammation will be reduced to a greater extent versus standard therapy. The methodology consisted of enrolling a minimum of 200 heart failure patients in various stages, from the whole spectrum of ejection fraction, and the results are compared with those emerged from literature and subsequently discussed.

Study objectives

This study aimed to demonstrate whether there is also a role in the inhibition of the systemic inflammatory response of these cardiac anti-remodeling drugs, and whether this effect further explains the role of these pharmacological classes in improving cardiac function and reducing patients' symptoms.

Research methodology

The selection of patients was done among patients diagnosed with chronic heart failure demonstrated by etiological context, physical examination, electrocardiogram and echocardiography, hospitalized in "Prof. Dr. Th. Burghele" Clinical Hospital for a period of 3 years: between January 2021 and March 2023.

The study is a retrospective longitudinal one, with patients from the whole spectrum of heart failure including: HFrEF (HF with reduced ejection fraction), HFmrEF (HF with mildly reduced ejection fraction) and HFpEF (HF with preserved ejection fraction). After adding them into the database in the Microsoft Excel program, a lot of patients was formed with several subgroups, which were analyzed through SPSS version 26 (SPSS Inc, Chicago IL).

Subgroup A: pacients with B or C AHA/ACC class of HF, irrespective of left ventricle ejection fraction (LVEF) which received one or more of the following classes of medication: beta-blockers (BB), angiotensin I converting enzyme inhibitors (ACE-I) / angiotensin II receptor blockers (ARB), mineralocorticoid antagonists (MRA).

Subgroup B: pacients with B or C AHA/ACC class of HF, irrespective of left ventricle ejection fraction (LVEF) which received one or both of the following classes of medication: sodium-glucose cotransporter 2 inhibitors (SGLT2i) and angiotensin II receptor blockers / neprilysin inhibitors (ARNI).

After the first assessment, patients in group A will be switched to the appropriate medication according to the 2021 ESC (European Society of Cardiology) heart failure guideline, updated in 2023, thus achieving a crossover in therapy between assessment times.

Candidates for inclusion in the protocol are patients in whom heart failure is confirmed by clinical, biological and imaging criteria and who meet the following inclusion criteria:

- Non-valvular B/C AHA/ACC classification HF patients, with II-IV NYHA functional class
- NT-proBNP>125 pg/ml
- Dyspnea +/- protodiastolic galop +/- turgescent jugular veins
- Patients aged between 18-90 years old

For these patients specific work-up investigation will be performed.

We will compare the inflammatory profile of CHF patients treated with ACE-I /ARB, BB, MRA and standard symptomatic medication (diuretics) with CHF subjects treated with ACE-I /ARB, BB, MRA, ARNI and SGLT2i and symptomatic treatment, at 2 evaluation moments (T0, T1).

A total of 220 patients with HF, regardless of ejection fraction, were included in the study. The distribution of patients within the cohort based on EF (reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction) was as follows: 111 patients with HFrEF, 23 patients with HFmrEF, and 86 patients with HFpEF.

All patients were enrolled at the first visit (T0) on guided-optimized medical therapy according to HF guidelines, at the maximum tolerated dose, regardless of whether this meant the addition of all anti-remodeling therapies (BB, ARNI/ACE-I/ARB, MRA, and SGLT2i), according to the EF phenotype, or increasing the dose from the aforementioned classes up to maximum tolerated one.

After a median of 6 months (T1) the patients were reevaluated with the same parameters, comparing the evolution between T0 and T1. For 123 cases, T1 was a routine assessment, while for 84 the second assessment was a decompensation of HF.

One of the limitations of this study is represented by the fact that despite the enrollment of a heterogeneous profile of patients, the study does not have randomization which can contribute to

a lower statistical power of the results. Also, the value of inflammatory markers could have been negatively influenced by the fact that for 84 patients the second assessment (T1) was during an acute HF decompensation, while for the other 123 it was a routine assessment. The proinflammatory markers used in the study (CRP, ESR [erythrocyte sedimentation rate] and fibrinogen) may also have been falsely elevated by another comorbidity that was decompensated at the time of evaluation. However, before starting the analysis, we excluded patients who, at the time of enrollment, were diagnosed with an infection, a condition indicated by leukocyturia, leukocytosis, or a positive urine culture.

Ethics approval and consent to participate

All patients have provided written informed consent for data collection and statistical analysis regarding the personal health parameters noted in the medical registries. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of "Prof. Dr. Th. Burghele" Clinical Hospital. (Bucharest, Romania; approval no. 3641/09.04.2024).

The structure of the chapters

The thesis is structured in 9 chapters, the general part includes Chapters 1, 2, 3 and 4, the special part includes Chapters 5, 6, 7 and 8, and Chapter 9 is represented by conclusions and personal contributions.

Chapter 1 is a prologue to CHF, presenting epidemiologic data, possible etiologies, the multitude of therapeutic options, and the prognosis of CHF. Representing a complex clinical syndrome that occurs as a result of a structural and/or functional impairment of the ejection and/or relaxation capacity of the left ventricle, CHF requires identification of the determining factor, as many etiologies benefit from specific treatment (18). For a treatment aligned to the ESC and AHA/ACC guidelines, correct definition and distinction based on ejection fraction between CHF phenotypes is necessary. The 3 CHF phenotypes are: HFrEF (heart failure with reduced ejection fraction) with EF (ejection fraction) ≤ 40%, HFmrEF (heart failure with mildly reduced ejection fraction) with EF 41-49% and HFpEF (heart failure with preserved ejection fraction) with EF ≥50%. From the point of view of epidemiological observational studies performed in hospitalized patients, approximately 50% of patients with CHF have HFrEF, and the rest have HFmrEF or

HFpEF. According to the ESC Long-Term Registry, among ambulatory patients with CHF: 60% have HFrEF phenotype, 24% HFmrEF, and 16% HFpEF (19). The risk factors that contribute to the establishment of CHF syndrome are cardiac and extracardiac in nature. Cardiac determinants include: ischemic heart disease (acute coronary syndrome or chronic coronary syndrome), valvulopathies, arrhythmias, cardiomyopathies, myocarditis, infective/non-infective endocarditis, endomyocardial diseases (endomyocardial fibrosis, endomyocardial eosinophilia), pericardial diseases (neoplastic pericarditis, tuberculous, uremic and the complicated form - constrictive pericarditis) and congenital heart diseases. Extracardiac risk factors are represented by: hypertension, diabetes, obstructive sleep apnea syndrome (OSA), systemic infectious diseases (Chagas disease, HIV infection, Lyme disease), infiltrative diseases (amyloidosis, sarcoidosis, secondary neoplastic determinations), storage diseases (hemochromatosis, Fabry disease, Gaucher disease), metabolic diseases, endocrine diseases, autoimmune diseases, neuromuscular pathologies (muscular dystrophies, Friedreich's ataxia), iatrogenic (radiotherapy, drugs: anthracyclines [doxorubicin], HER2 inhibitors [trastuzumab], checkpoint inhibitors [nivolumab], VEGF inhibitors [bevacizumab], proteasome inhibitors [bortezomib], RAF+MEK inhibitors) (20).

Chapter 2 presents data on the pathophysiology of CHF, as a prototype of organ disease – systemic disease – neuroendocrine disease. A series of both laboratory and clinical evidence suggest that the development and progression of CHF are based on the excessive synthesis of some molecules with biologically active effect. These molecules produce, by direct and indirect mechanisms (involving certain intracellular signalling pathways), deleterious effects in the heart and central and peripheral circulation. The multitude of mechanisms and systems involving such molecules include: activation of the sympathetic nervous system (SNS) and activation of the renin-angiotensin-aldosterone system (RAAS) which try to maintain an adequate stroke volume under conditions of volume overload (sodium and water retention). In addition to these two essential mechanisms in the generation of CHF, peripheral arterial vasoconstriction and the multitude of inflammatory mediators join, as part of the systemic inflammatory response of CHF. All these mechanisms are responsible for the cardiac remodeling that occurs in CHF. This complex network of biologically active molecules that are synthesized within the CHF is known as neurohormonal model and is the current theory explaining the generation of CHF (1).

Subchapter 2.2. displays the pro-inflammatory cytokines that are part of the chronic inflammatory infiltrate present in CHF. Although activated at a relatively low-grade level

compared to infectious pathologies or autoimmune diseases, the positive feedback loop that maintains this stimulation determines the persistence of chronic inflammation. The main pro-inflammatory cytokines are: TNF alpha, IL-1, IL-6, IL-8, IL-18, IL-33, MPO (myeloperoxidases), iNOS (inducible nitric oxide synthase) and CRP (21,22).

Chapter 3 includes clinical, biological and imagistic criteria for the diagnosis of CHF (23–26).

Chapter 4 includes data regarding the multimodal treatment of CHF. This principles of treatment are composed of non-pharmacological measures (dietary recommandations, light to moderate aerobic physical activity), pharmacological treatment, invasive treatment (electrophysiological and/or angiographic) and cardiovascular surgery (implantation of mechanical assist devices of the ventricle and the last form in the terminal stages – heart transplantation) (18). The medication classes used in the treatment of HFrEF are: BB, ACE-I/ARB, MRA, ARNI și SGLT2i, while in the cases of HFmrEF and HFpEF the treatment consists only in SGLT2i, the only antiremodeling class which is included in the guideline across the entire spectrum of EF. The antiremodeling treatment are joined by symptomatic treatment (diuretics: loop diuretics and thiazide diuretics) aimed to reduce the congestion syndrome (27,28).

Subchapter 5.1. presents the research hypothesis and the objective of the doctoral research study.

Subchapter 5.2. is represented by the material and method, also including the statistical analysis method, which was performed in the SPSS program version 26 (SPSS Inc, Chicago IL).

Chapter 6 presents the descriptive statistics data of the study. It includes a cohort of 220 patients of whom: 111 belong to HFrEF phenotype, 23 to HFmrEF and 86 to HFpEF.

Chapter 7 presents the results of analytical statistics, presented in tables and figures and explained. The chapter is composed of 4 subchapters which are tailored on the 4 hypotheses of the research.

Subcapitolul 7.1. is represented by the Ist Hypothesis, which examined whether there is a statistically significant association between heart failure markers (HF) and inflammation markers, more specifically whether certain heart failure related variables are associated with reduced inflammation markers between T0 and T1. In order to test this hypothesis, the inflammation markers used were: CRP, ESR, and fibrinogen which were recorded at T0 and T1. Clinical

symptoms, biological investigations, as well as imaging investigations were used for the evaluation of CHF.

In order to eliminate the possible hazard of another cause of inflammation that could alter the associations observed in this research, it was decided to exclude patients who had at T0 or T1 CRP, ESR and fibrinogen values higher than the value corresponding to mean + 3 standard deviations . More precisely, the following exclusion criterion were used: CRP greater than 100 mg/l, or ESR greater than 120 mm/h, or fibrinogen greater than 700 mg/dl. Of the total of 220 participating patients, 13 patients met this criteria, taking into account their exclusion from analyzes of inflammatory markers, as well as the dynamic of these markers from T0 to T1.

A significant correlation was observed between the dynamics of CRP and the presence of AMI in the antecedents of the patients and the existence of diastolic dysfunction (delayed relaxation type). In the case of ESR, a significant correlation was observed with the presence of anasarca in patients. And in the case of fibrinogen, a correlation was observed between the dynamics of this inflammation marker and the presence of dilated cardiomyopathy with or without ventricular gallop at the objective examination.

Subchapter 7.2. The IInd hypothesis tested the role of medication in association with markers of inflammation and clinical parameters of heart failure. More specifically, it tested whether patients who received SGLT2i and/or ARNI in combination with standard medication had lower levels of inflammatory markers at T1 compared to patients who received standard medication alone. A marginally significant result in CRP reduction between T0 and T1 was observed in patients receiving ARNI and/or SGLT2i. Comparatively, patients who did not receive any of these drug classes had an increase in CRP at the time of reassessment.

Also, patients who received SGLT2i had a statistically significant reduction in fibrinogen values between T0 and T1, compared to the other drug classes.

Subchapter 7.3. The IIIrd hypothesis examined whether there are differences between the three heart failure subgroups (HFrEF, HFmrEF and HFpEF) in terms of the dynamics of inflammation markers and NT-proBNP, and in correlation with the type of medication received. The results showed that patients who did not receive diuretics benefited from a decrease in CRP values regardless of EF, whereas patients with reduced and preserved EF who took diuretics had increased CRP values at T1 compared with T0. Based on estimated means, fibrinogen values were

shown to decrease in patients receiving SGLT2i regardless of EF type, whereas for patients not receiving SGLT2i, fibrinogen values increased among patients with HFpEF and remained approximately constant in patients with HFrEF. In contrast, fibrinogen decreased between assessments in HFrEF patients who did not receive a diuretic, but increased in those who did. However, fibrinogen remained approximately constant in HFmrEF patients who did not receive a diuretic, but decreased in those who received a diuretic.

In subchapter 7.4., the IVth hypothesis looked at whether there were differences between different doses of medication prescribed at T0, in terms of the impact on inflammation markers.

In the case of BB, there was a different dynamic of the ESR values between T0 and T1, in patients who received carvedilol in therapy. In the case of low (6.25 mg, bi daily) and medium (12.5 mg, bi daily) dose of carvedilol a reduction in the values of ESR was observed, compared to patients who received the high dose (25 m, bi daily), where an increase in ESR levels was observed. There were no significant differences between BB doses in terms of CRP or fibrinogen dynamics.

For the doses of ACE-I, ARB and MRA, no statistically significant results were identified in the dynamics of any inflammation marker (CRP, ESR, fibrinogen) between the two evaluation moments.

In the case of ARNI, statistically significant results were obtained in association with the dynamics of the CRP values between T0 and T1. In the case of patients who did not receive ARNI or received the 24/26 mg dose (bi daily), the CRP values increased between T0 and T1. However, in the case of patients who received the dose of 49/51 mg (bi daily) or 97/103 mg (bi daily), statistically significant reductions of CRP values were observed in the dynamics. No significant results were observed for the correlation between ARNI dose and ESR or fibrinogen dynamics.

In the case of SGLT2i, no significant results were obtained in association with the dynamics of CRP, ESR or fibrinogen values.

Chapter 8 includes discussions comparing the results of the present research and other studies in the specialized literature.

In this study, a trend towards a reduction in mean CRP levels was observed in patients who received both ARNI and SGLT2i in the HF regimen (but with only marginal statistical significance, p=0.054). Conversely, an increase in mean CRP values was observed in patients who did not receive ARNI and/or SGLT2i. Regarding serum fibrinogen levels, we observed a significant

reduction in fibrinogen levels in patients receiving SGLT2i (p=0.022), but also a significant increase after diuretic treatment (p=0.011).

According to a systematic review and meta-analysis, SGLT2i led to a reduction in inflammation in laboratory animal studies, lowering the levels of IL-6, CRP, and TNF alpha (29).

Another study conducted by Benedikt et. al (2023) evaluated patients who had suffered an acute myocardial infarction, looking at the impact of SGLT2i (empagliflozin) on inflammatory biomarkers. This was a post-hoc analysis of the EMMY trial. The study showed a reduction in hsCRP (hypersensitive C reactive protein) and IL6 levels after 26 weeks of follow-up, but without reaching statistical significance between empagliflozin and the placebo group (p values being 0.52 and 0.65, respectively) (30,31).

These results are similar to the trend of decreased in CRP values after SGLT2i treatment between T1 and T0 in our study, but in this case the result was only marginally significant, p being 0.054.

ARNI has also been studied for its anti-inflammatory effect in heart failure patients. Goncalves et. al, evaluated the effect of ARNI on CRP levels. The results showed a significant reduction in CRP value after 6 months of treatment (p=0.014) (32).

In our study, patients who received only ARNI from the 3 subgroups (patients treated with only ARNI, only with SGLT2i, or both) had the greatest reduction in CRP, compared with patients who did not receive ARNI and/or SGLT2i.

In the 4th hypothesis, our research evaluated the effects of BB, ACE-I, ARB, MRA, SGLT2i and ARNI on 3 intensively used markers of non-specific systemic inflammation (CRP, ESR and fibrinogen) in clinical practice. We compared different doses of each active substance in those drug classes, and then compared the active substances within the class to each other to observe their effects on the dynamics of inflammatory biomarkers.

Of the beta-blocker class, carvedilol achieved a significant reduction in ESR levels from T0 to T1 (p=0.049). The dynamics of ESR was different for each dose of carvedilol: at the low dose (6.25 mg, bi daily), ESR values decreased from 33.70 mm/h to 18.39 mm/h; and for the dose of 12.5 mg (bi dialy), the ESR values decreased the most, from 22.58 mm/h to 7.59 mm/h. However, for the 25 mg dose (bi daily), ESR values increased slightly, from 16.78 mm/h to 20.31 mm/h.

In a sub-analysis of the BRIGHT-D trial, two beta-blockers, bisoprolol and carvedilol, reduced hsCRP, with the former having a greater effect (from 3.35 ng/ml to 2.69 ng/ml, p=0.001) compared to carvedilol (from 3.38 ng/ml to 2.85 ng/ml, p=0.047) (33). The same conclusion was obtained also by Bagatomo et. al, in another study (34).

Jenkins et. al, showed a reduction in CRP level in patients with HF of ischemic etiology who received BB, compared to those who did not (-1.2 mg/l mean CRP level for the BB group, p<0.001) (35).

In our research, where 170 patients were treated with BB (115-metoprolol succinate, 18 bisoprolol, 37 carvedilol), none influenced CRP and fibrinogen levels.

However, carvedilol achieved a significant reduction in ESR levels from T0 to T1 (p=0.049), an effect seen in the low (6.25 mg, bi daily) and medium (12.5 mg, bi daily) doses.

A study by Goncalves et. al, evaluating patients with HF receiving ARNI, demonstrated a significant reduction in CRP levels (from 2.5 mg/l to 2.2 mg/l, p=0.014) (32).

Also, in our study, patients who received ARNI (N=30) had a statistically significant decrease in CRP levels from baseline (p=0.004). This result was obtained in the subgroup of patients with medium (49/51 mg, bi daily; N=17 patients) and high doses (97/103 mg, bi daily; N=7 patients), while in the subgroup of patients with a low dose (24/26 mg, bi daily; N=6 patients) an opposite effect, of a slight increase in CRP, was observed.

Regarding the SGLT2i class, a meta-analysis evaluating the anti-inflammatory effect of SGLT2i on CRP in experimental models revealed a reduction in CRP levels (mean reduction of -2.17 mg/l; [95% CI; -2 .80 mg/l to -1.53 mg/l]) (29). A reduction in CRP value was also observed by Wang et. al, in a study of patients with type 2 diabetes who received SGLT2i (36).

In our study, 33 patients received an SGLT2i (31-dapagliflozin and 2 empagliflozin) as part of their treatment. However, no significant decrease in CRP, ESR, or fibrinogen values was observed between T0 and T1.

Conclusions

The studied drug therapy was based on the 2021 ESC treatment guidelines of CHF, updated in 2023, and the 2022 AHA/ACC guideline. These indicate the classes of anti-remodeling drugs which showed a reduction in mortality and rehospitalization risk among these patients. Also, the guideline included the diuretics with C level of evidence, as symptomatic therapy, with effect in reducing congestion.

1. In the comparative analysis between inflammatory biomarkers and the CHF phenotypes (HFrEF, HFmrEF, HFpEF), there was a correlation between CRP, ESR and fibrinogen levels and HFmrEF patients. This subgroup of patients was followed by the HFpEF phenotype of patients, while the HFrEF patients had the lowest levels of CRP, ESR and fibrinogen. However, in the case of decompensated CHF patients, the HFmrEF patients showed the most stable profile of inflammatory biomarkers (the lowest elevation, from T0) in comparison to HFpEF and HFrEF patients.

2. From the beta-blockers evaluated bisoprolol and metoprolol, no significant result was obtained in the impact on the values of CRP, VSH or fibrinogen.

3. In the case of carvedilol the doses of 6.25 mg (bi daily) and 12.5 mg (bi daily) showed a significant reduction of the ESR value (p=0,049). For patients with 25 mg (bi daily) dose, and those who did not receive carvedilol, an increase in the ESR values was observed upon re-evaluation.

4. ACE-I, ARB or MRA did not significantly change the values of CRP, ESH or fibrinogen between assessments.

5. ARNI was correlated with a reduction in the CRP value (p=0,004) in the dose of 49/51 mg (bi daily) and 97/103 mg (bi daily). An increase in CRP was observed in sacubitril/valsartan 24/26 mg (bi daily) and patients who did not receive ARNI.

6. There is a trend toward a reduction in CRP in patients receiving ARNI and/or SGLT2i.

7. SGLT2i showed statistically significance in reducing the levels of fibrinogen in dynamics (p=0,022), however the diuretics were correlated with an increase in the levels of fibrinogen in dynamics.

8. Compliance to CHF guidelines should be mandatory at any time during the evolution of the pathology, with the aim of reaching the highest tolerated dose for a maximal effect.

Personal contributions

1. We studied the literature, identifying the data that emphasize the participation of proinflammatory cytokines and inflammation markers in CHF. We drew an overall picture collecting all the data and showcasing the impact of inflammatory markers on cardiomyocytes.

2. We examined whether there is a statistically significant association between markers of heart failure (HF) and inflammation. For this aim we evaluated the correlation between the inflammatory makers' (CRP, ESH and fibrinogen) dynamics and clinical, paraclinical and imaging signs of HF.

3. We investigated the effect of new anti-remodeling drug classes (ARNI and SGLT2i) on systemic inflammation compared to classical anti-remodeling drug classes (BB, ACE-I, ARB, MRA) and also to diuretics and statins.

4. We examined whether there are differences between the 3 phenotypes of HF (HFrEF, HFmrEF, and HFpEF) regarding the dynamics of inflammation markers and NT-proBNP. We subsequently evaluated whether the reduction of systemic inflammation by anti-remodeling active substances is achieved differently depending on the CHF phenotype.

5. We studied whether there were differences between the different doses of medication prescribed at the time of enrollment, in terms of the impact on inflammatory markers and whether the reduction in their values is achieved linearly (the higher the dose of the active substance, the greater the reduction in markers' values).

6. The results of statistical analysis from our study, show that the classic anti-remodeling medication against CHF (BB, ACE-I/BRA, MRA) accompanied by symptomatic therapy (diuretics) did not significantly reduce the systemic inflammation. In contrast, the new classes of anti-remodeling medication from the CHF guideline (ARNI +/- SGLT2i) showed an important trend in the reduction of inflammatory biomarkers, with marginal significant results ($p=0.054$), both in monotherapy, as well as in combined therapy.

Bibliography

1. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol [Internet]. 2017 Dec 12 [cited 2023 Nov 6];14(1):30–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27708278/

2. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol [Internet]. 2009 Jul 28 [cited 2023 Nov 6];54(5):375–85. Available from: https://pubmed.ncbi.nlm.nih.gov/19628111/

3. Guang C, Phillips RD, Jiang B, Milani F. Three key proteases--angiotensin-I-converting enzyme (ACE), ACE2 and renin--within and beyond the renin-angiotensin system. Arch Cardiovasc Dis [Internet]. 2012 Jun [cited 2023 Nov 6];105(6–7):373–85. Available from: https://pubmed.ncbi.nlm.nih.gov/22800722/

4. Torre-Amione G, Kapadia S, Lee J, Durand JB, Bies RD, Young JB, et al. Tumor Necrosis Factor-α and Tumor Necrosis Factor Receptors in the Failing Human Heart. Circulation [Internet]. 1996 Feb 15 [cited 2023 Nov 6];93(4):704–11. Available from: https://www.ahajournals.org/doi/abs/10.1161/01.cir.93.4.704

5. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol [Internet]. 2013 Jul 23 [cited 2023 Nov 6];62(4):263–71. Available from: https://pubmed.ncbi.nlm.nih.gov/23684677/

6. Satyajeet S Rathi, Yan-Jun Xu, Naranjan S Dhalla. Experimental and Clinical Cardiology. 2002 [cited 2023 Nov 6]. p. 146–50 Mechanism of cardioprotective action of TNF-alpha in the isolated rat heart - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/19649239/

7. Szekely Y, Arbel Y. A Review of Interleukin-1 in Heart Disease: Where Do We Stand Today? Cardiol Ther [Internet]. 2018 Jun 1 [cited 2023 Nov 6];7(1):25–44. Available from: https://pubmed.ncbi.nlm.nih.gov/29417406/

8. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol [Internet]. 1998 Feb [cited 2023 Nov 6];31(2):391–8. Available from: https://pubmed.ncbi.nlm.nih.gov/9462584/

9. De Gennaro L, Brunetti ND, Montrone D, De Rosa F, Cuculo A, Di Biase M. Subacute inflammatory activation in subjects with acute coronary syndrome and left ventricular dysfunction. Inflammation [Internet]. 2012 Feb [cited 2023 Nov 6];35(1):363–70. Available from: https://pubmed.ncbi.nlm.nih.gov/21487907/

10. Mallat Z, Corbaz A, Scoazec A, Besnard S, Lesèche G, Chvatchko Y, et al. Expression of interleukin-18 in human atherosclerotic plaques and relation to plaque instability. Circulation [Internet]. 2001 Oct 1 [cited 2023 Dec 8];104(14):1598–603. Available from: https://europepmc.org/article/MED/11581135

11. Segiet OA, Piecuch A, Mielańczyk Ł, Michalski M, Nowalany-Kozielska E. Role of interleukins in heart failure with reduced ejection fraction. Anatol J Cardiol [Internet]. 2019 Nov 1 [cited 2023 Nov 6];22(6):287–99. Available from: https://doaj.org/article/c4dc4ee1851a44a5b973337f4bb251d6

12. Pollheimer J, Bodin J, Sundnes O, Edelmann RJ, Skånland SS, Sponheim J, et al. Interleukin-33 drives a proinflammatory endothelial activation that selectively targets non-quiescent cells. Arterioscler Thromb Vasc Biol [Internet]. 2013 Feb [cited 2023 Nov 6];33(2). Available from: http://atvb.ahajournals.org/lookup/suppl/doi:10.1161/ATVBAHA.112.253427/-/DC1.

13. Sheriff A, Kayser S, Brunner P, Vogt B. C-Reactive Protein Triggers Cell Death in Ischemic Cells. Front Immunol [Internet]. 2021 Feb 10 [cited 2023 Nov 6];12. Available from: https://pubmed.ncbi.nlm.nih.gov/33679775/

14. Michelucci A, Ricciardi G, Sofi F, Gori AM, Pirolo F, Pieragnoli P, et al. Relation of inflammatory status to major adverse cardiac events and reverse remodeling in patients undergoing cardiac resynchronization therapy. J Card Fail [Internet]. 2007 Apr 1 [cited 2023 Dec 9];13(3):207–10. Available from: https://europepmc.org/article/MED/17448418

15. Torzewski J, Fan J, Schunkert H, Szalai A, Torzewski M. C-reactive protein and arteriosclerosis. Mediators Inflamm [Internet]. 2014 [cited 2023 Dec 9];2014. Available from: https://pubmed.ncbi.nlm.nih.gov/24976688/

16. Tziomalos K, Hare JM. Role of xanthine oxidoreductase in cardiac nitroso-redox imbalance. Front Biosci (Landmark Ed) [Internet]. 2009 Jan 1 [cited 2023 Nov 6];14(1):237–62. Available from: https://pubmed.ncbi.nlm.nih.gov/19273066/

17. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med [Internet]. 2015 Jun 1 [cited 2023 Nov 6];175(6):996–1004. Available from: https://pubmed.ncbi.nlm.nih.gov/25895156/

18. McDonagh TA, Metra M, Adamo M, Baumbach A, Böhm M, Burri H, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J [Internet]. 2021 Sep 21 [cited 2024 Apr 17];42(36):3599–726. Available from: https://dx.doi.org/10.1093/eurheartj/ehab368

19. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail [Internet]. 2017 Dec 1 [cited 2023 Nov 6];19(12):1574–85. Available from: https://pubmed.ncbi.nlm.nih.gov/28386917/

20. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet [Internet]. 2018 Nov 10 [cited 2023 Nov 6];392(10159):1789–858. Available from: https://pubmed.ncbi.nlm.nih.gov/30496104/

21. Reina-Couto M, Pereira-Terra P, Quelhas-Santos J, Silva-Pereira C, Albino-Teixeira A, Sousa T. Inflammation in Human Heart Failure: Major Mediators and Therapeutic Targets. Front Physiol [Internet]. 2021 Oct 11 [cited 2023 Nov 6];12. Available from: https://pubmed.ncbi.nlm.nih.gov/34707513/

22. Reina-Couto M, Vale L, Carvalho J, Bettencourt P, Albino-Teixeira A, Sousa T. Resolving Inflammation in Heart Failure: Novel Protective Lipid Mediators. Curr Drug Targets [Internet]. 2016 Jul 12 [cited 2023 Nov 6];17(10):1206–23. Available from: https://pubmed.ncbi.nlm.nih.gov/26721409/

23. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail [Internet]. 2010 May [cited 2023 Nov 6];12(5):423–33. Available from: https://pubmed.ncbi.nlm.nih.gov/20354029/

24. Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, et al. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. Circ Heart Fail [Internet]. 2011 Jul 8 [cited 2023 Nov 6];4(5):628–36. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21743005/?tool=EBI

25. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Soci. J Am Soc Echocardiogr [Internet]. 2011 Mar [cited 2023 Nov 6];24(3):229–67. Available from: https://pubmed.ncbi.nlm.nih.gov/21338862/

26. Ridgway JP. Cardiovascular magnetic resonance physics for clinicians: part I. J Cardiovasc Magn Reson [Internet]. 2010 [cited 2023 Nov 6];12(1). Available from: https://pubmed.ncbi.nlm.nih.gov/21118531/

27. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2022 May 3 [cited 2023 Nov 6];145(18):E895–1032. Available from: https://pubmed.ncbi.nlm.nih.gov/35363499/

28. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J [Internet]. 2023 Oct 1 [cited 2024 Apr 17];44(37):3627–39. Available from: https://dx.doi.org/10.1093/eurheartj/ehad195

29. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis K, et al. The impact of SGLT2 inhibitors on inflammation: A systematic review and meta-analysis of studies in rodents. Int Immunopharmacol. 2022 Oct 1;111:109080.

30. Benedikt M, Mangge H, Aziz F, Curcic P, Pailer S, Herrmann M, et al. Impact of the SGLT2-inhibitor empagliflozin on inflammatory biomarkers after acute myocardial infarction – a post-hoc analysis of the EMMY trial. Cardiovasc Diabetol [Internet]. 2023 Dec 1 [cited 2024 May 3];22(1):1–11. Available from: https://cardiab.biomedcentral.com/articles/10.1186/s12933-023-01904-6

31. Tripolt NJ, Kolesnik E, Pferschy PN, Verheyen N, Ablasser K, Sailer S, et al. Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction—The EMMY trial. Am Heart J. 2020 Mar 1;221:39–47.

32. Goncalves AV, Pereira-da-Silva T, Galrinho A, Rio P, Branco LM, Soares R, et al. C-reactive protein reduction with sacubitril-valsartan treatment in heart failure patients. Am J Cardiovasc Dis [Internet]. 2020 [cited 2024 Apr 17];10(3):174. Available from: /pmc/articles/PMC7486532/

33. Toyoda S, Haruyama A, Inami S, Arikawa T, Saito F, Watanabe R, et al. Effects of carvedilol vs bisoprolol on inflammation and oxidative stress in patients with chronic heart failure. J Cardiol [Internet]. 2020 Feb 1 [cited 2024 Apr 17];75(2):140–7. Available from: https://pubmed.ncbi.nlm.nih.gov/31444140/

34. Nagatomo Y, Yoshikawa T, Kohno T, Yoshizawa A, Anzai T, Meguro T, et al. Effects of beta-blocker therapy on high sensitivity c-reactive protein, oxidative stress, and cardiac function in patients with congestive heart failure. J Card Fail [Internet]. 2007 Jun [cited 2024 Apr 17];13(5):365–71. Available from: https://pubmed.ncbi.nlm.nih.gov/17602983/

35. Jenkins NP, Keevil BG, Hutchinson I V., Brooks NH. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. American Journal of Medicine [Internet]. 2002 [cited 2024 Apr 17];112(4):269–74. Available from: https://pubmed.ncbi.nlm.nih.gov/11893365/

36. Wang D, Liu J, Zhong L, Li S, Zhou L, Zhang Q, et al. The effect of sodium-glucose cotransporter 2 inhibitors on biomarkers of inflammation: A systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2022 Nov 11;13:1045235.

List with scientific articles published

1. Review article: **"Inflammation in Heart Failure—Future Perspectives"** Journal of Clinical Medicine (revistă indexată ISI; IF-3,9) 2023, 12(24), 7738; https://doi.org/10.3390/jcm12247738 (Q2 – capitolul 4, pag 34-39)

   Arvunescu, A.M.; Ionescu, R.F.; Cretoiu, S.M.; Dumitrescu, S.I.; Zaharia, O.; Nanea, I.T. Inflammation in Heart Failure—Future Perspectives. Journal of Clinical Medicine (revistă indexată ISI; IF-3,9) 2023, Vol. 12 (24), 7738; doi:10.3390/JCM12247738

2. Original article: **"Guideline-Optimised Treatment in Heart Failure—Do Higher Doses Reduce Systemic Inflammation More Significantly?"** Journal of Clinical Medicine (revistă indexată ISI; IF-3,9) 2024, 13(11), 3056; https://doi.org/10.3390/jcm13113056 (Q2 – capitolul 7.4, pag 117-127)

   Arvunescu, A.M.; Ionescu, R.F.; Dumitrescu, S.I.; Zaharia, O.; Nanea, I.T. Guideline-Optimised Treatment in Heart Failure—Do Higher Doses Reduce Systemic Inflammation More Significantly? Journal of Clinical Medicine (revistă indexată ISI; IF-3,9) 2024, 13(11), 3056; doi:10.3390/jcm13113056

3. Original article: **„The real-world anti-inflammatory effect of SGLT2i in patients with chronic heart failure"** Journal of Medicine and Life 2025, 18(2), 155-164; doi: 10.25122/jml-2025-0011; https://pmc.ncbi.nlm.nih.gov/articles/PMC11932508/ (capitolul 7.3, pag 110-116)

Arvunescu, A.M.; Ionescu, R.F.; Dumitrescu, S.I.; Zaharia, O.; Nanea, I.T. The real-world anti-inflammatory effect of SGLT2i in patients with chronic heart failure. Journal of Medicine and Life 2025, 18(2), 155-164; doi:10.25122/jml-2025-0011;