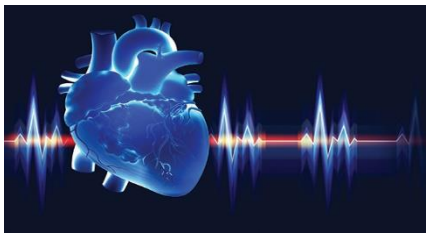
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ - ΚΑΡΔΙΟ-ΟΓΚΟΛΟΓΙΑ - ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ»

(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)



Μεταπτυχιακή Διπλωματική Εργασία

«Φλεγμονή και Καρδιακή Ανεπάρκεια»

υπό

Κυριάκου Ανδρέα

Ειδικευόμενος Καρδιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Καρδιακή ανεπάρκεια – Καρδιο-ογκολογία – Καρδιαγγειακή αποκατάσταση»

Λάρισα, Φεβρουάριος 2025

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ - ΚΑΡΔΙΟ-ΟΓΚΟΛΟΓΙΑ - ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ»

(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)

Inflammation and Heart Failure

Larissa, February 2025

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας».

Υπογραφή:

ΚΥΡΙΑΚΟΥ ΑΝΔΡΕΑΣ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2025

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

ΙΩΑΝΝΗΣ ΣΚΟΥΛΑΡΙΓΚΗΣ

ΚΑΘΗΓΗΤΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΘΕΣΣΑΛΙΑΣ

Επιβλέπων:

Σκουλαρίγκης Ιωάννης, Καθηγητής Καρδιολογίας, Τμήματος Ιατρικής Πανεπιστημίου Θεσσαλίας

Τριμελής Εξεταστική Επιτροπή:

1. Σκουλαρίγκης Ιωάννης, *Καθηγητής Καρδιολογίας, Τμήματος Ιατρικής Πανεπιστημίου Θεσσαλίας- (Επιβλέπων)*
2. Παπαμιχάλης Μιχάλης, *Επιμελητής Α' Καρδιολογίας, Πανεπιστημιακό Νοσοκομείο Λάρισας*
3. Τσαρούχας Κωνσταντίνος, *Επιμελητής Α' Καρδιολογίας, Πανεπιστημιακό Νοσοκομείο Λάρισας*

Αναπληρωματικό μέλος:

Γιαμούζης Γρηγόριος, *Αναπληρωτής Καθηγητής Καρδιολογίας, Τμήματος Ιατρικής Πανεπιστημίου Θεσσαλίας*

Inflammation and Heart Failure

Ευχαριστίες

Με το πέρας της μεταπτυχιακής διπλωματικής μου εργασίας, είναι υποχρέωση μου να ευχαριστήσω θερμά τον επιβλέποντα Καθηγητή μου, κύριο Σκουλαρίγκη Ιωάννη για το ενδιαφέρον, τις υποδείξεις του και την επιστημονική του καθοδήγηση.

Επίσης θα ήθελα να ευχαριστήσω θερμά τον σύμβουλο της διπλωματικής μου εργασίας, κύριο Παπαμιχάλη για τις απαραίτητες υποδείξεις του, τις συμβουλές και τη διαθεσιμότητα του κατά τη διάρκεια αυτού του τριμήνου μέχρι και την ολοκλήρωση της εργασίας.

Τέλος ρόλο συμπαράστασης και στήριξης σε όλο αυτό το διάστημα των σπουδών μου είχε η οικογένεια και η σύζυγος μου στους οποίους είμαι ευγνώμων.

ΚΥΡΙΑΚΟΥ ΑΝΔΡΕΑΣ

Περίληψη

Τίτλος: Φλεγμονή και Καρδιακή Ανεπάρκεια

Εισαγωγή: Η καρδιακή ανεπάρκεια αποτελεί μία από τις σημαντικότερες αιτίες νοσηρότητας και θνησιμότητας σε παγκόσμιο επίπεδο, ασκώντας σημαντική επιβάρυνση στα συστήματα υγείας. Τα τελευταία χρόνια, η φλεγμονή έχει αναγνωριστεί ως ένας από τους βασικούς παράγοντες που επηρεάζουν την εξέλιξη της νόσου, συμβάλλοντας στην επιδείνωση της λειτουργίας του μυοκαρδίου. Η αλληλεπίδραση μεταξύ της συστηματικής φλεγμονής, των κυτταροκινών και των μεταβολικών διαταραχών οδηγεί σε προοδευτικές δομικές και λειτουργικές αλλαγές της καρδιάς.

Σκοπός: Ο σκοπός της εργασίας είναι να αναδείξει τη σημασία της φλεγμονής στην καρδιακή ανεπάρκεια, να αξιολογήσει τις υπάρχουσες διαγνωστικές και θεραπευτικές στρατηγικές και να προσδιορίσει τις ερευνητικές κατευθύνσεις που απαιτούνται για τη βελτίωση της πρόγνωσης των ασθενών.

Μεθοδολογία: Για την εκπόνηση της παρούσας ανασκόπησης, πραγματοποιήθηκε αναζήτηση της βιβλιογραφίας σε έγκριτες βάσεις δεδομένων, όπως το PubMed και το Google Scholar. Αναλύθηκαν μελέτες που εξετάζουν τις φλεγμονώδεις διαδικασίες στην καρδιακή ανεπάρκεια, τη μιτοχονδριακή δυσλειτουργία, την ανάπτυξη νέων βιοδεικτών και τις σύγχρονες θεραπευτικές επιλογές.

Αποτελέσματα: Η φλεγμονή φαίνεται να παίζει καταλυτικό ρόλο στην παθογένεση της καρδιακής ανεπάρκειας, επηρεάζοντας δυσμενώς τη λειτουργία του μυοκαρδίου. Οι βιοδείκτες, και ιδιαίτερα οι κυτταροκίνες, έχουν τη δυνατότητα να συνεισφέρουν στη διάγνωση, στην σταδιοποίηση στην πρόγνωση της νόσου, ωστόσο η αξιοποίησή τους στην κλινική πράξη παραμένει περιορισμένη. Οι αντιφλεγμονώδεις παράγοντες, οι αντιοξειδωτικές θεραπείες και οι ρυθμιστές της μιτοχονδριακής λειτουργίας έχουν δείξει ελπιδοφόρα αποτελέσματα σε κλινικές δοκιμές, ωστόσο απαιτούνται περισσότερες μελέτες για την πλήρη τεκμηρίωση της αποτελεσματικότητάς τους.

Συμπέρασμα: Η κατανόηση της φλεγμονής ως θεμελιώδους παράγοντα της καρδιακής ανεπάρκειας αποτελεί βασικό βήμα για την ανάπτυξη στοχευμένων θεραπειών. Παρά την πρόοδο στον τομέα των βιοδεικτών και των θεραπευτικών στρατηγικών, υπάρχει ανάγκη για περαιτέρω έρευνα με στόχο την εξατομικευμένη αντιμετώπιση των ασθενών και τη βελτίωση της ποιότητας ζωής τους.

Λέξεις-κλειδιά: Φλεγμονή, Καρδιακή Ανεπάρκεια, Παθοφυσιολογία, Βιοδείκτες, Θεραπεία

Abstract:

Title: Inflammation and Heart Failure

Background: Heart failure (HF) is a major global health challenge and remains one of the leading causes of morbidity and mortality. Over recent years, inflammation has been recognized as a critical factor in HF pathophysiology, contributing to myocardial dysfunction and disease progression. The interplay between systemic inflammation, cytokine signalling, and metabolic dysregulation leads to structural and functional myocardial changes. These multifaceted mechanisms highlight the complexity of HF and emphasize the need for more effective diagnostic and therapeutic strategies.

Objective: This thesis aims to comprehensively analyse the role of inflammation in HF, emphasizing its impact on disease progression, biomarker discovery, and emerging therapeutic approaches. By reviewing recent advancements, the study seeks to identify gaps in knowledge and explore potential future directions in HF management.

Methods: A thorough literature review was conducted using reputable scientific databases such as PubMed and Google Scholar. Studies focusing on the inflammatory mechanisms of HF, mitochondrial dysfunction, biomarker development, and novel therapeutic interventions were examined.

Results: Inflammatory processes play a pivotal role in HF progression, influencing myocardial remodelling and metabolic regulation. Despite the identification of promising biomarkers for diagnosis and risk stratification, their routine clinical implementation remains limited. Therapies targeting inflammation and mitochondrial function, including cytokine inhibitors, calcium modulators, and antioxidant agents, have shown encouraging results in preclinical and clinical studies. However, the heterogeneous nature of HF underscores the need for personalized therapeutic approaches, as trial outcomes have often been inconsistent.

Conclusion: Inflammation is a fundamental component of HF pathophysiology, and its modulation presents a promising avenue for improving patient care. Advances in biomarker identification and targeted therapies offer new opportunities to enhance diagnosis and treatment. Nevertheless, further research is needed to translate these findings into personalized treatment strategies, ultimately improving quality of life and clinical outcomes for HF patients.

Key words: Inflammation, Heart Failure, Pathophysiology, Biomarkers, Treatment

CONTENTS:

Introduction

HF is a complex clinical syndrome characterized by symptoms and signs resulting from any structural or functional impairment of ventricular filling or blood ejection (1). HF is currently classified based on left ventricular ejection fraction (LVEF) into three primary categories: heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with reduced ejection fraction (HFrEF). This classification facilitates tailored treatment approaches, as each category is associated with distinct pathophysiological mechanisms, clinical outcomes, and variations in patient prognosis and response to therapy. Data indicate that HF is a major and growing public health issue worldwide. It is a leading cause of morbidity, frequent hospitalization, and high mortality, particularly among older adults. In developed countries, HF remains the primary cause of hospitalization for patients over 65, imposing substantial healthcare costs and resource demands. Despite treatment advances, prognosis remains poor, with a five-year mortality rate comparable to that of some groups of cancer. Although HF incidence is stable, prevalence is expected to rise due to the ageing population and the improvement in medical therapies, which will likely further increase hospitalization rates and health care costs (2). As a result, HF represents a critical focus for healthcare systems, underscoring the need for improved preventive strategies, early detection, and innovative therapeutic approaches to mitigate its impact.

The involvement of inflammation in the onset and progression of HF has been proposed for many years. Numerous researches have indicated that various cytokines and chemokines may play a role in both acute and chronic HF, although early therapeutic trials targeting these pathways have yielded inconsistent outcomes. These findings emphasize the complexity and intricate nature of how pro-inflammatory pathways influence HF pathogenesis. Latest research has revealed that inflammation may have apparent roles depending on HF syndrome phenotypes, insights that could inform the development of new therapeutic approaches (3).

This thesis aims to provide an in-depth analysis of the relationship between heart failure (HF) and inflammation, addressing the significant role inflammation plays in both the onset and progression of HF. Inflammatory mediators have been implicated in the development of HF, influencing processes that lead to cardiac dysfunction, remodeling,

and fibrosis. This interconnected relationship suggests that HF and inflammation do not merely coexist; rather, they are interdependent, with inflammatory mechanisms actively participating in HF progression and exacerbation. Consequently, inflammation may not only serve as a biomarker of disease severity but could also represent a potential target for therapeutic intervention.

Pathophysiology of Heart Failure

As mentioned above HF is classified into three subtypes: HFrEF, HFmrEF and HFpEF. HFrEF occurs when the heart muscle weakens, typically due to ischemic heart disease or dilated cardiomyopathy, leading to an important reduction in ejection fraction during systole. Conversely, HFpEF involves a preserved ejection fraction but impaired ventricular filling, often associated with conditions like hypertension, diabetes, and obesity, causing diastolic dysfunction. Understanding these subtypes is crucial, as their distinct pathophysiological mechanisms lead to differences in clinical presentation, treatment responses, and prognosis. This introduction lays the groundwork for a detailed exploration of the pathophysiology of HF.

HFrEF is more prevalent in men than in women and is associated with considerable morbidity and mortality. Recent years have seen notable scientific advancements in the treatment of HFrEF. Despite these developments, morbidity and mortality remain elevated, with a five-year survival rate of only 25% following hospitalization (4). On the other side, there is HFpEF, which is a critical aspect of HF, carrying substantial morbidity and mortality too. Unlike HFrEF, however, there are currently no validated, efficient therapies for HFpEF. Key contributors to HFpEF include aging, diabetes mellitus (DM), obesity, systemic hypertension, coronary artery disease, metabolic syndrome, and kidney disease. In diagnosing HFpEF, it is essential to rule out similar conditions, including non-HF disorders and other causes of HF with an LVEF ≥50%, such as valvular heart disease, pericardial disease and types of cardiomyopathies (5). Healthcare systems worldwide are facing an urgent need to understand the underlying mechanisms of heart failure. In response to declining function, the failing heart activates various compensatory mechanisms. These include the Frank-Starling mechanism, which enhances cardiac

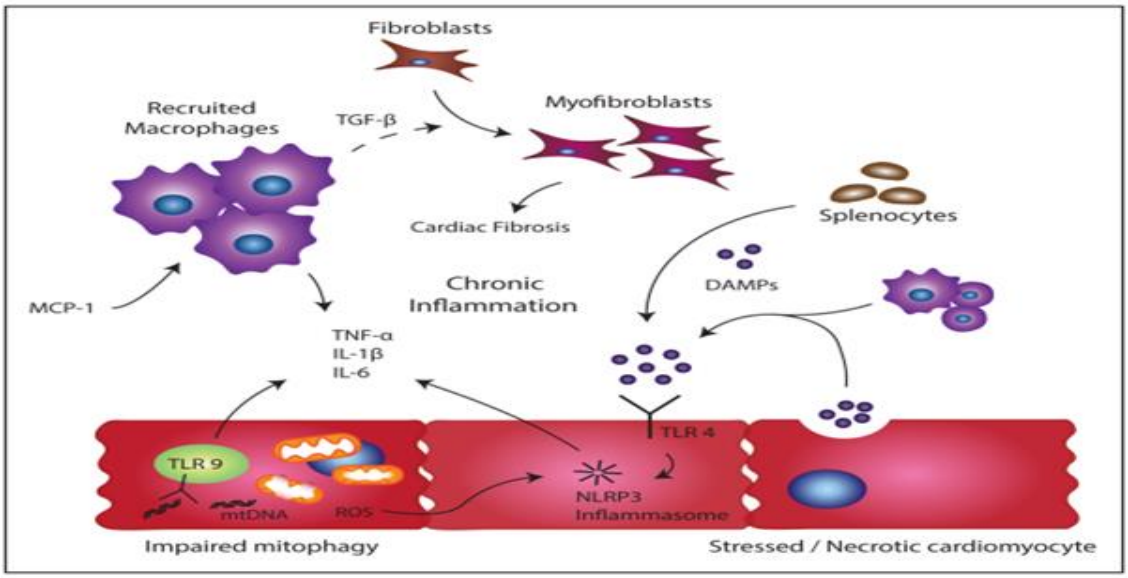
output; ventricular remodeling, leading to thickening of the ventricular walls; and activation of neurohormonal systems, which work to maintain tissue perfusion despite increased mean arterial pressure. While compensatory mechanisms offer initial benefits in the early stages of HF, they frequently lead to a detrimental cycle that accelerates disease progression. The establishment of the neurohormonal model of HF, which includes activation of both the sympathetic nervous system (SNS) and the renin-angiotensin system (RAAS), has played a pivotal role in advancing scientific understanding and clinical research into the physiology and treatment of heart failure (6). As far as SNS is concerned, it initially supports the failing heart by enhancing contractility to boost stroke volume and causing peripheral vasoconstriction to preserve mean arterial pressure. However, this response eventually contributes to worsening disease and decreases survival rates. SNS activation is believed to stem from diminished inhibitory controls and increased excitatory signals, involving changes in baroreceptor and chemoreceptor reflexes in the periphery, chemical mediators that influence sympathetic activity, and central integration sites (7). A crucial role in the development of HF maintains RAAS. Excessive activation of RAAS, particularly the overactivation of Angiotensin II and Aldosterone, can promote the development of heart failure through various mechanisms (6). For example, it leads to an imbalance in fluid and electrolyte regulation, increased vascular resistance, and fibrosis, all of which exacerbate the strain on the heart and impair its function. Persistent activation of this system has a detrimental impact on not only the cardiovascular system but also the kidneys, promoting renal dysfunction and further complicating heart failure.

Inflammatory Pathways in Heart Failure

In both HFrEF, regardless of ischemic or nonischemic origins, and HFpEF, elevated serum levels of proinflammatory cytokines are associated with poorer clinical outcomes. Although cytokine elevations in chronic heart failure (CHF) are generally lower than those observed in acute infections or autoimmune diseases, this persistent low-grade inflammatory state may play an important role in the progressive worsening of HF symptoms. Chronic inflammation is believed to contribute to deleterious processes such as cardiac remodeling, endothelial dysfunction, and impaired myocardial function, each

of which exacerbates the severity of heart failure. Thus, advancing our understanding of the impact of sustained, low-grade inflammation in heart failure could identify novel therapeutic targets aimed at reducing inflammation to improve clinical outcomes for patients (8).

As mentioned above, chronic, low-grade, systemic inflammation might have harmful effects on myocardial structure and function (9). The predominant hypothesis detailing the pathway by which inflammation promotes the onset and progression of HF is presented in the image below (this pathway has yet to be fully validated in animal models of chronic HF).



(8) **Fig. 1** The pathway of Chronic Inflammation

CHF may be driven by various mechanisms that stimulate the release of inflammatory cytokines. Cardiomyocytes can become activated in response to damage-associated molecular patterns (DAMPs), such as extracellular HSP60 (heat shock protein 60) and HMGB1 (high-mobility group box 1), which are released from immune cells (macrophages/monocytes), splenocytes, or damaged/stressed cardiomyocytes. These DAMPs signal through Toll-like receptor 4 (TLR4), activating the NLRP3 inflammasome and leading to the secretion of proinflammatory cytokines. Oxidative stress and reactive oxygen species (ROS), particularly in the context of DM, can also activate the NLRP3 inflammasome. Furthermore, impaired mitophagy allows damaged mitochondria to release mitochondrial DNA (mtDNA), which in turn stimulates cytokine production via TLR9 signaling. This inflammatory environment facilitates the recruitment of

macrophages, mediated by monocyte chemoattractant protein 1 (MCP-1), which further supports cytokine release. Cardiac macrophages additionally contribute to the recruitment and differentiation of myofibroblasts, which promote cardiac fibrosis in chronic HF. This fibrosis process is thought to involve transforming growth factor (TGF)-β. IL stands for interleukin, and TNF for tumor necrosis factor.

Mitochondria-Inflammation axis

The heart is an organ with an exceptionally high energy demand, relying primarily on adenosine triphosphate (ATP) production through oxidative phosphorylation within the mitochondria. These organelles, often referred to as the "power plants" of the cell and occupying nearly one-third of cellular volume, play a pivotal role in maintaining cardiac function (10). Regardless of the underlying cause, mitochondrial dysfunction has been extensively recognized as a key factor in the progression of HF.

In HF, disruptions in mitochondrial function hinder oxidative phosphorylation, a vital mechanism for efficient ATP synthesis. Pathological remodeling of the heart prompts a metabolic transition from fatty acid oxidation to glycolysis, a less efficient pathway for meeting the heart’s substantial energy needs. This shift results in energy shortages that worsen cardiac impairment (11). Moreover, enzyme hyperacetylation within mitochondria interferes with substrate oxidation, further reducing energy output and aggravating the deterioration of cardiac performance.

Mitochondria are essential for maintaining calcium homeostasis, a process critical for cardiomyocyte excitation-contraction coupling and relaxation. They regulate calcium ion movement between the sarcoplasmic reticulum, cytosol, and mitochondria, ensuring efficient cardiac function. In heart failure, disruptions in calcium handling, including impaired reuptake by the sarcoplasmic reticulum and increased leakage, lead to cytosolic and mitochondrial calcium overload. This imbalance triggers mitochondrial dysfunction, oxidative stress, reduced contractile efficiency, and heightened susceptibility to arrhythmias, ultimately contributing to cardiomyocyte death and disease progression (12).

Furthermore, in the context of HF, the overproduction of mitochondrial-derived reactive oxygen species (mtROS) exacerbates oxidative stress and triggers inflammation. MtROS are capable of initiating proinflammatory signaling cascades and stimulating the release

of mitochondrial DNA (mtDNA) and other DAMPs, further escalating the inflammatory response (13). The oxidative harm caused by mtROS disrupts mitochondrial activity, creating a harmful cycle of mitochondrial impairment and heightened ROS production, leading to HF worsening.

Biomarkers in Heart Failure

Biomarker profiles vary significantly across the range of EF (3). A network meta-analysis examining biomarkers in heart failure indicated that individuals with HFrEF primarily demonstrated a "cardiac stretch" profile, marked by biomarkers linked to cellular proliferation and metabolic activity (14). In contrast, biomarkers in HFpEF were largely associated with cardiac inflammation, with patients presenting a broader spectrum of biomarkers that mirror their heterogeneous clinical manifestations.

C-reactive protein

C-reactive protein (CRP) is a well-established plasma marker that rises substantially during acute inflammation, infection, or tissue damage. It is predominantly synthesized by hepatocytes, with its production being regulated at the post-transcriptional level by cytokines, especially interleukin-6 (IL-6) (15). CRP has been identified as a possible indicator of adverse outcomes in patients with heart failure. Comparable findings are observed when examining the relationship between high-sensitivity CRP (hs-CRP) levels and adverse heart failure events. Elevated baseline hs-CRP levels independently predicted increased all-cause and cardiovascular mortality (16). It has yet to be determined whether targeting the inflammatory pathways influencing CRP levels could enhance clinical outcomes in heart failure patients.

Uric Acid

Uric acid (UA) is the final product of purine metabolism in humans, mainly controlled by the enzyme xanthine oxidoreductase, which facilitates the conversion of hypoxanthine to xanthine and xanthine to UA (17). In CHF, hyperuricemia serves as a marker of disrupted oxidative metabolism, hyperinsulinemia, inflammatory cytokine activation (especially TNF-α), and impaired vascular function (18). This, consequently, plays a role in the development of cardiac hypertrophy and fibrosis.

Leukocytes

Leukocyte indices, including the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and pan-immune inflammation value (PIV), are promising biomarkers of systemic inflammation. Neutrophils are a significant part in the pathogenesis of HF and have a well-established association with the severity of HF and overall mortality in patients with various heart failure etiologies. In particular, NLR is significantly linked to clinical outcomes in patients with new-onset or worsening HFrEF and HFpEF. Additionally, NLR showed a significant correlation with several established biomarkers related to inflammatory pathways in HF and is notably correlated with NT-proBNP levels. Furthermore, a reduction in NLR after six months was associated with a decreased incidence of mortality and heart failure-related hospitalizations (19). Although MLR has not been extensively studied, several associations with heart failure are described in the literature. Elevated MLR provides significant predictive value when incorporated into a detailed clinical risk prediction model for forecasting heart failure hospitalizations after CABG. It is also strongly associated with the risk of future heart failure admissions in patients with CAD (20). Finally, PIV is a promising biomarker in relation to inflammation and heart failure. The Pan-Immune-Inflammation Value (PIV) is calculated using the formula: PIV = [Neutrophil count ($\times 10^9$/L) × Platelet count ($\times 10^9$/L) × Monocyte count ($\times 10^9$/L)] ÷ Lymphocyte count ($\times 10^9$/L) (21). In both patients with acute decompensated HFrEF and those undergoing percutaneous coronary intervention for ST-segment elevation myocardial infarction, the PIV may serve as a prognostic marker, providing valuable information (22). These three biomarkers are independently linked with a composite endpoint, including all-cause mortality and heart failure-related hospitalizations, as well as with all-cause mortality specifically in those

diagnosed with HFpEF, providing valuable prognostic insight. However, their full prognostic significance is yet to be completely understood.

Systemic inflammatory response index

The Systemic Inflammatory Response Index (SIRI) is calculated by multiplying the neutrophil and monocyte counts, then dividing the product by the lymphocyte count (23). Elevated SIRI levels are strongly associated with increased all-cause mortality in patients with HFpEF, with the risk escalating alongside rising SIRI levels. Its prognostic value becomes even more pronounced when combined with traditional risk factor models, enhancing the precision of mortality and outcome predictions (24).

Angiotensin-converting enzyme 2 (ACE-2) and renin–angiotensin aldosterone system biomarkers

Endothelial activation and the infiltration of inflammatory cells are key factors in the development of cardiac fibrosis induced by the renin–angiotensin system (25). ACE-2 catalyzes the conversion of angiotensin II (Ang II) into angiotensin 1–7 (Ang 1–7), which counteracts the molecular and cellular effects of Ang II. The reduction of ACE-2 activity increases the risk of HF, whereas elevated levels of ACE-2 can prevent and reverse the heart failure phenotype. ACE-2 and Ang 1–7 have been identified as critical components of a protective pathway in both HFrEF and HFpEF since they maintain strong anti-inflammatory, antioxidant, anti-fibrotic, and vasodilatory effects (26). Levels of Ang 1–7 or Ang II alone do not show prognostic value. However, the plasma ratio of Ang 1–7 to Ang II has been identified as a significant predictor of all-cause mortality and the length of hospitalization in patients with HF (27).

Natriuretic Peptides

Natriuretic peptides (NP), synthesized by the heart, play a vital protective role by facilitating processes such as sodium excretion, increased urine production, and blood vessel relaxation. Additionally, they contribute to improved heart muscle relaxation, fat metabolism, weight management, and better insulin sensitivity, highlighting their multifaceted benefits in maintaining cardiovascular and metabolic health (28). B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are commonly recognized as neurohormonal biomarkers. Inflammation appears to enhance NP release,

but the interpretation of NP levels should account for other factors contributing to inflammation (29).

Inflammatory Cytokines

Numerous cytokines play a pivotal role in the pathogenesis of HF. Patients with HF often exhibit elevated levels of pro-inflammatory and anti-inflammatory cytokines, as well as their corresponding receptors. These increases emphasize the critical role of inflammation in the progression and pathophysiology of HF (30). Particular emphasis should be given to interleukin-1β (IL-1β), a pro-inflammatory cytokine, involved in adverse cardiac remodeling (31). Elevated IL-1β levels have been linked to the severity of HF, as indicated by the New York Heart Association (NYHA) functional classification system. Furthermore, interleukin-6 (IL-6) is a cytokine whose plasma concentrations are independently linked to higher mortality rates and/or heart failure hospitalizations. These findings underscore IL-6's crucial role in risk assessment for heart failure, providing initial evidence that supports further investigation into the potential therapeutic benefits of modulating IL-6 signaling (32).

Soluble toll-like receptor 2

Soluble suppression of tumorigenesis-2 (sST2) has been recognized as a significant biomarker that reflects the underlying pathophysiology of HF and provides valuable insight into the disease's progression, clinical status and prognosis (33). sST2 belongs to the family of IL-1 receptors and is released in response to vascular congestion and both inflammatory and pro-inflammatory stimuli (34). In CHF, elevated levels of sST2 have been linked to left ventricular (LV) diastolic dysfunction, increased right ventricular systolic pressure (RVSP), and reduced myocardial contractility. Furthermore, sST2 levels have been observed to be higher in patients experiencing ventricular arrhythmias compared to those without such events. In cases of acute HF, it is advisable to measure sST2 levels at least at the time of admission and again prior to planned discharge. Persistent elevation of sST2 levels may indicate a higher risk profile for the patient, potentially warranting an extended hospital stay, expedited titration of HF medication and more frequent follow-ups or the use of monitoring systems to detect early pulmonary congestion (35).

Galectin-3

Galectin-3 (Gal-3) is a β-galactoside-binding lectin that has garnered considerable attention as a biomarker in HF. Beyond its diagnostic and prognostic applications, Gal-3 plays a critical role in the pathophysiology of HF by mediating pro-inflammatory responses and driving fibrotic processes. It is implicated in critical mechanisms such as macrophage activation, extracellular matrix remodeling, and tissue repair, all of which contribute to the progression and severity of HF (36). Importantly, Gal-3 retains significant prognostic value, even when adjusted for other established risk factors, and serves as an independent predictor of mortality in HF patients (37).

Growth/differentiation factor 15

Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine classified within the transforming growth factor-β (TGF-β) group, recognized for its significance in cellular stress signaling and inflammatory regulation (38). It is a versatile biomarker that holds potential as a prognostic indicator across various clinical conditions and outcomes (39). There is considerable evidence supporting the role of GDF-15 as a standalone predictor of overall mortality in HF. Furthermore, it may enhance risk prediction for both HF and mortality in individuals recovering from a myocardial infarction (40). The predictive power of GDF-15 is strengthened when used alongside other biomarkers. A model that incorporates both NT-pro BNP and GDF-15 could enhance treatment strategies focused only on BNP, offering improved forecasts for all-cause mortality and heart failure rehospitalizations over a one-year period (41).

Clonal hematopoiesis of indeterminate significance

Clonal Hematopoiesis of Indeterminate Potential (CHIP) refers to the age-associated acquisition of somatic mutations in hematopoietic stem cells that lead to the expansion of distinct blood cell clones (42). The occurrence of CHIP becomes more common with advancing age. Its frequency remains low from birth to around 50 years old, but it escalates sharply thereafter. Moreover, CHIP is associated with a heightened risk of developing atherosclerotic cardiovascular disease (CVD) (43) and is potentially associated with the progression and adverse outcomes of CHF, particularly in cases with an ischemic background (44). Research indicates that CHIP could represent a significant new age-related risk factor for HF.

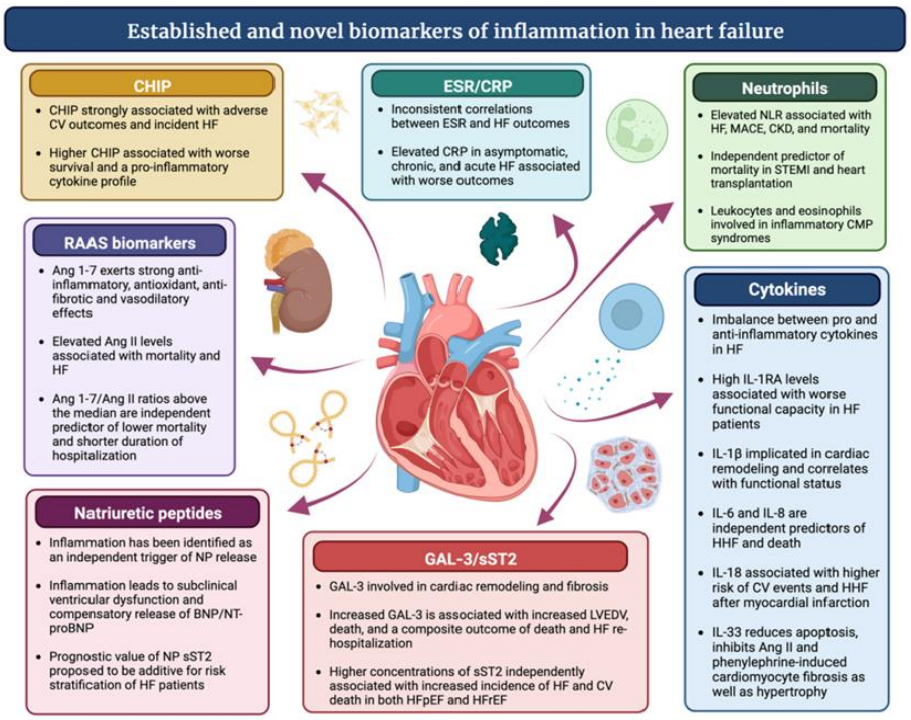


Fig. 2

Established and Novel Biomarkers of Inflammation in HF. (3)

Current Therapeutic Approaches and Inflammatory Targets

Despite growing evidence emphasizing the role of inflammatory pathways in the pathophysiology of HF, effective therapeutic strategies targeting inflammation remain largely unavailable. Current HF treatments primarily focus on neurohormonal modulation and hemodynamic support, leaving the inflammatory component insufficiently addressed. However, recent advancements have been made in the development of such therapies, and several promising pharmaceutical approaches are now emerging.

Established HF Therapies:

Renin-angiotensin-aldosterone system Blockers

Renin-angiotensin-aldosterone system (RAAS) blockade is a cornerstone in HF management (45). In HFrEF, these therapies improve survival, reduce hospitalizations, and alleviate symptoms by mitigating maladaptive neurohormonal activation (46). However, their utility in HFpEF is limited, as current evidence does not support their routine use to improve outcomes in this population (47). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) possess notable anti-

inflammatory properties, including the ability to decrease the production of reactive oxygen species, pro-inflammatory cytokines, and cellular adhesion molecules. Turning theory into data, the use of ACE inhibitors in patients with HFrEF results in a statistically significant reduction in hs-CRP and NT-proBNP levels. Furthermore, in a prospective observational study involving 507 patients who experienced their first ischemic stroke, ACE inhibitor therapy was associated with a 2.6-fold decrease in median CRP levels and a reduced 2-year CV risk (48). Another important pillar in the treatment of HF, included in RAAS, is Mineralocorticoid Receptor Antagonists (MRAs). MRAs prevent aldosterone from attaching to mineralocorticoid receptors (49). The actions of aldosterone are detrimental and involve the stimulation of fibrosis, the initiation of inflammation, and the production of oxidative stress (50). The role of MRAs in reducing inflammatory biomarkers remains contentious. Findings from the TOPCAT biorepository indicate that spironolactone therapy effectively lowers BNP and NT-proBNP levels. However, it does not appear to significantly affect cardiac troponin I (cTnI), hs-CRP, or uric acid concentrations (51).

Beta Blockers

Beta blockers (BBs) function by inhibiting β-adrenergic receptors (52). Like RAAS blockade, BBs play a crucial role in the treatment of HFrEF. However, their effectiveness and utility in treating HFmrEF and HFpEF remain uncertain (53). Regarding inflammation, BBs exhibit neutral effects. Research indicates that BBs can lower circulating TNF-alpha levels in patients with dilated cardiomyopathy (DCM), a reduction closely linked to changes in circulating IL-10 levels (54). A comparable decrease in TNF-alpha and IL-6 levels has also been observed in individuals with ischemic cardiomyopathy (55). This data is derived from studies with small sample sizes, and for this reason, definitive conclusions cannot be reliably drawn. Although BBs positively influence clinical outcomes, myocardial performance, and reverse remodeling, their impact on pro-inflammatory markers has been minimal or negligible.

Sodium-Glucose Co-Transporter 2 Inhibitors

Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors have recently emerged as a promising therapeutic option for HF. Initially approved for managing type-2 diabetes mellitus (T2DM), these agents have now become a cornerstone in HF treatment, irrespective of EF. Their primary mechanism involves reducing glucose reabsorption in

the kidneys, thereby promoting increased glucose excretion (56). SGLT2 inhibitors seem to mitigate inflammation through multiple mechanisms. A study involving 30 diabetic mice demonstrated that the SGLT2 inhibitor empagliflozin effectively reduces myocardial fibrosis by primarily inhibiting collagen production and deposition via the classical TGF-β/Smad signaling pathway, while also alleviating oxidative stress (57). At the same time, multiple studies have revealed that SGLT2 inhibitors positively influence pro-inflammatory cytokines, including IL-6, TNF-α and IFN-γ (58). Although there are considerable gaps in our understanding of SGLT2 inhibitors and their anti-inflammatory effects, their impact on patients with HF is undeniable and substantial.

Diuretics

Diuretics are fundamental in HF management, serving as the cornerstone treatment for relieving fluid overload in HF patients (59). While not part of the guideline-recommended treatment (GDMT) for HF (1), they are deemed essential for enhancing the quality of life in patients with HF, both during acute episodes and in the chronic phase. Research indicates that diuretics may have a protective role in mitigating or halting the progression of inflammation. While the precise mechanism of their action is not fully understood, they seem to reduce the levels of inflammatory mediators such as TNF-α, IL-6, IL-2 (60).

Heart Failure and Anti-Inflammatory Agents:

Statins

Statins rank among the most potent therapies for managing and preventing atherothrombotic vascular disorders. Beyond their lipid-lowering properties, their ability to suppress inflammation has been extensively validated through both clinical trials and experimental investigations (61). Statin treatment demonstrated a notable correlation with enhanced adjusted survival rates in individuals with HFpEF and ischemic HF. Nevertheless, this association was not recorded in patients with HFrEF suffering from non-ischemic HF (62). Furthermore, statins have been shown to reduce CRP levels, a reduction often independent of cholesterol lowering, and appear to exert beneficial effects on endothelial function, monocyte-macrophage activity, and platelet aggregation, all of which further contribute to their cardiovascular benefits (63).

Colchicine

Colchicine is a mitotic inhibitor that disrupts tubulin polymerization and prevents microtubule formation. Consequently, its anti-inflammatory properties may partly stem from its capacity to block NLRP3 inflammasome assembly, thereby indirectly suppressing interleukin-1β activation. This, in turn, leads to subsequent reductions in interleukin-6 levels and CRP concentrations (64). The COLCOT and LoDoCo trials have highlighted the potential benefits of colchicine in cardiovascular disease management. The COLCOT trial investigated the effects of colchicine at a daily dose of 0.5 mg compared to placebo over two years in 4,745 post-myocardial infarction (MI) patients. The study demonstrated a significant reduction in the composite primary endpoint, which included MI, stroke, resuscitated cardiac arrest, urgent hospitalization for angina requiring revascularization, and cardiovascular mortality (65). Similarly, the LoDoCo trial demonstrated that low-dose colchicine reduced major adverse CV events in patients with chronic coronary disease (66). A total of 5,522 participants were randomized, with 2,762 allocated to the colchicine group and 2,760 to the placebo group. The median follow-up period spanned 28.6 months. The primary endpoint encompassed a composite of CV death, spontaneous (non-procedural) MI, ischemic stroke, or coronary revascularization driven by ischemia. The key secondary endpoint included a composite of CV death, spontaneous MI, and ischemic stroke (67). Both studies underscore colchicine's anti-inflammatory properties, offering promising evidence for its role in secondary CV prevention. While research suggests that colchicine's anti-inflammatory effects may reduce markers like CRP and IL-6, definitive evidence supporting its long-term benefit in enhancing the functional status of HF patients remains lacking (68). The COLpEF trial (NCT04857931), a current randomized study, is investigating the potential of colchicine to alleviate inflammation, enhance left ventricular diastolic function, and improve both functional capacity and symptoms in individuals with HFpEF. The trial is expected to offer additional insights into the therapeutic role of colchicine in HFpEF management. Careful consideration is required for individuals with severe renal impairment, as the prolonged use of colchicine, which relies on renal clearance, may not be appropriate for this population.

Methotrexate

Methotrexate is a potent FDA-approved folate antagonist primarily prescribed for rheumatoid arthritis (69). Due to its systemic anti-inflammatory capacity and its ability to slow the progression of atherosclerosis, methotrexate is associated with a reduced cardiovascular risk in patients with immune-mediated inflammatory conditions (70), while incorporating methotrexate into standard treatment for CHF yields notable anti-inflammatory benefits and enhances NYHA functional class, 6-minute walk test performance, and quality of life (71). Further research is needed to explore methotrexate's potential in reducing inflammation and improving outcomes in HF.

Anti TNF-alpha Factors

TNF-alpha is a pro-inflammatory cytokine involved in many inflammatory pathways and linked to adverse effects on cardiac contractility. It is generated under various pathological conditions, including septic shock, acute myocarditis and congestive HF (72). Serum concentrations of TNF-alpha are elevated in HF patients and the degree of this increase is strongly associated with the severity of the condition (73). To counteract its harmful effects, anti-TNF-alpha agents have been developed and widely used. Agents, including infliximab, adalimumab, etanercept, and certolizumab are used to manage inflammatory conditions by targeting and neutralizing TNF-alpha activity. Etanercept and infliximab are the two agents studied in HF, primarily in HFrEF, with the goal of mitigating inflammation, improving clinical outcomes, and potentially enhancing patients' overall functional capacity. According to the RENEWAL trial, etanercept failed to show any significant advantage in managing patients (74). Similarly, in the ATTACH trial, infliximab administration failed to improve clinical outcomes in heart failure patients across a range of evaluations. Specifically, in those with at least moderate chronic heart failure, treatment with infliximab resulted to a decline in clinical condition, greater hospitalization risk, and frequent exacerbations of HF, with no substantial clinical benefits observed over a 6-week treatment period (75). Although anti-TNF alpha agents failed to demonstrate efficacy in these studies, they have not been tested in patients with HFpEF, in whom they may potentially show greater effectiveness. Therefore, studies involving such patients could provide valuable insights into their application in HF.

Interleukin-1 inhibitors

IL-1, as mentioned before, is significantly upregulated in HF and is correlated with an unfavorable prognosis (76). IL-1 inhibitors, such as Anakinra and Canakinumab, have been investigated in clinical trials involving patients with HF to evaluate their potential in reducing inflammation and improving cardiac outcomes. The D-HART trial administered Anakinra to 12 patients with HFpEF and elevated CRP levels over a 14-day period. Peak VO2, widely recognized as the gold standard for assessing functional capacity and a strong prognostic indicator in HF, was selected as the primary endpoint. A reduction in CRP levels, indicative of decreased IL-1 activity, was closely associated with improvements in peak VO2. The impact of Anakinra on HFrEF patients was minimal. The findings demonstrated that Anakinra effectively reduced systemic inflammation and improved aerobic exercise capacity in these patients (77). Conversely, the DHART-2 trial investigated the use of Anakinra in 31 individuals with HF and obesity, reporting no significant enhancement in peak VO_2 or VE/VCO_2. These findings occurred despite observed decreases in hsCRP and NT-proBNP levels, as well as improved exercise tolerance (78). Moreover, the CANTOS trial was developed to investigate the inflammatory theory of atherothrombosis and was performed on a distinct population of individuals with HF - patients with a history of myocardial infarction and signs of systemic inflammation, indicated by increased hs-CRP levels. The administration of Canakinumab (150 mg every three months) led to a notable reduction in baseline hs-CRP levels and was linked to a substantial decrease in the recurrence of CV events (Myocardial Infarction, Stroke and CV death) compared to “placebo-patients” (79). Most of the patients included in this trial exhibited characteristics such as obesity, diabetes, and hypertension, which align them with the HFpEF group. While Canakinumab was not ultimately approved for secondary CV prevention, the CANTOS trial provided compelling evidence that targeting the inflammatory pathway involving the NLRP3 inflammasome and IL-1β can effectively reduce CV events and offer potential benefits for patients with HFpEF (80). Nevertheless, additional research is necessary to reach more conclusive and reliable findings regarding both Anakinra and Canakinumab.

Interleukin-6 Inhibitors

IL-6 is a multifunctional cytokine involved in immune defense and the acute-phase response. While essential for fighting infections and facilitating tissue repair, excessive

IL-6 production contributes to inflammatory conditions, including cytokine storms, and is implicated in various chronic diseases. IL-6 inhibitors, such as tocilizumab and ziltivekimab, mitigate these effects by blocking IL-6 signaling, reducing inflammation and immune dysregulation (81). The RESCUE trial demonstrated that Ziltivekimab significantly reduced inflammatory biomarkers, such as hsCRP and NLR, as well as thrombotic biomarkers associated with atherosclerosis, without the adverse effects typically observed with other agents in its class, supporting further cardiovascular outcomes research (82). The ongoing ZEUS trial aims to assess whether these anti-inflammatory effects translate into reduced cardiovascular events and slowed kidney dysfunction in 6,000 patients with atherosclerosis, chronic kidney disease (CKD), and elevated hsCRP levels (83). Besides ZEUS trial, the administration of Ziltivekimab will be assessed in HERMES trial. This trial investigates the impact of a monthly 15mg dose of Ziltivekimab, administered additionally to standard care, compared to a placebo. The primary focus is on the composite outcome of time to the first CV death, HF hospitalization, or urgent HF visit in patients with HFpEF or HFmrEF. The study plans to enroll 5,600 participants with a LVEF greater than 40%, moderately elevated NT-proBNP levels, at least one echocardiographic abnormality and hsCRP ≥2 mg/l.

Myeloperoxidase Inhibitors

Myeloperoxidase (MPO) is an enzyme primarily localized in neutrophils and monocytes, essential components of the immune system. Byproducts of MPO activity, such as hypochlorous acid, contribute to oxidative tissue damage, which is closely associated with inflammatory and cardiovascular disorders and the progression of HF (84). Elevated MPO levels are frequently related with worse clinical outcomes in HF patients. (85). Given MPO's significant involvement in inflammation and oxidative damage, it is being actively studied as a potential therapeutic target. AZD4831 is a cutting-edge covalent inhibitor specifically designed with high precision to target MPO, showcasing exceptional selectivity and promising potential as a therapeutic option for conditions involving oxidative stress and inflammation. Its function is irreversible (86). According to the SATELLITE trial, MPO inhibitors hold promise for patients with HFpEF or HFmrEF. This study utilized three distinct HFpEF cohorts to investigate the relationships between proteomic biomarkers and clinical outcomes, such as hospitalizations, mortality, functional capacity (measured by 6-minute walk distance (6MWD)), and quality of life (87). Although MPO inhibition represents an innovative approach for HFpEF, further

research is essential to fully assess its effectiveness and broaden our understanding of its therapeutic potential in this context. The ongoing ENDEAVOR trial shows promise in evaluating the potential of MPO inhibition to enhance symptoms and exercise capacity in individuals with HFpEF and HFmrEF (88).

Mitochondria-Inflammation Axis Therapies

Calcium homeostasis is essential for maintaining mitochondrial function, making it a critical target in HF therapies. Strategies focusing on calcium regulation have shown promise in preclinical and clinical settings. Inhibitors of mitochondrial sodium-calcium exchangers and inhibitors of the sarcolemma sodium-calcium exchangers might demonstrate potential in improving cardiac function in preclinical HF models. Omecamtiv mecarbil, a myosin activator that enhances calcium sensitivity in myofilaments (89), has been extensively studied. In the ATOMIC-HF trial, intravenous administration showed safety in acute HF patients, with some positive effects at higher doses (90). Additionally, the COSMIC-HF trial revealed that oral omecamtiv mecarbil improved cardiac function over 20 weeks, with benefits persisting even after discontinuation, indicating sustained therapeutic effects (91).

Gaining deeper insights into mtROS signaling is crucial for developing therapies targeting mito-inflammatory diseases. Mitochondrial antioxidants have emerged as potential therapeutic agents in HF, aiming to reduce oxidative stress and protect mitochondrial function, thereby improving cardiomyocyte survival and overall cardiac performance. MitoTEMPO and MitoQ have shown protective effects against HF and reperfusion injury.

Complementary Lifestyle Interventions:

Exercise

The available research includes only a small number of randomized controlled trials investigating the effects of exercise on inflammation, particularly in individuals with HF. Moreover, the outcomes of these studies often lack clear conclusions. Impaired exercise capacity is a major concern for individuals with HFpEF, contributing to diminished quality of life and poorer clinical outcomes (92). Data from small observational studies

reveal a connection between self-reported physical activity levels and inflammatory biomarkers, indicating that physical activity might help reduce chronic inflammation. Additionally, some randomized controlled trials suggest the potential of aerobic exercise to lower inflammation, particularly in individuals with chronic conditions and elevated inflammatory markers (93). TNF-alpha and IL-6 are two inflammatory biomarkers that have demonstrated significant reductions in individuals with HF (94). Further research is required to clarify the impact of exercise on patients with HF. Exercise should be personalized for each patient. Therefore, questions regarding exercise in HF, such as the optimal type, duration, and intensity of exercise, required to achieve meaningful clinical outcomes need to be addressed.

Diet and Microbiome-Based Therapies

Proper nutrition plays a crucial role in reducing systemic inflammation in HF patients. Dietary modifications can enhance metabolic health, strengthen antioxidant defenses, and regulate inflammatory pathways, potentially improving clinical outcomes. For example, Trimethylamine N-oxide (TMAO), a microbial metabolite produced in the gut, is elevated after consuming L-carnitine and phosphatidylcholine-rich foods. TMAO has been related with increased inflammation, and a dose-dependent relationship exists between plasma TMAO levels, cardiovascular events, and mortality (95). Another important aspect of nutrition that plays a significant role in HF is iron deficiency. Iron deficiency is commonly associated with a lot of diseases characterized by inflammatory activation. Research, including clinical trials and meta-analyses, has demonstrated that treating iron deficiency in HF patients can enhance quality of life, lower hospitalization rates, and reduce mortality (96). However, further investigation is necessary to draw definitive conclusions. The FAIR-HF2 trial (NCT03036462) is an active study aimed at investigating the impact of intravenous iron therapy on hospitalizations due to HF and CV mortality.

Challenges and Future Directions

HF remains a significant global health challenge, and inflammation plays a critical role in its pathophysiology. Despite advances in understanding this relationship, significant gaps persist. The complex interplay between inflammatory pathways and the progression

of HF is not fully elucidated. For instance, the precise mechanisms by which proinflammatory cytokines such as TNF-alpha, IL-1 and IL-6 contribute to myocardial remodeling, contractile dysfunction, and systemic complications are still under investigation. Additionally, while systemic inflammation is widely recognized as a contributor to HF progression, the specific triggers for chronic inflammation in HF patients—including the roles of comorbid conditions like obesity, diabetes, and hypertension — remain poorly defined.

Current pharmacological strategies targeting inflammation in HF have yielded mixed results, highlighting notable gaps in treatment efficacy. Anti-TNF-α therapies such as etanercept and infliximab, while initially promising, failed to demonstrate clinical benefit in large trials and, in some cases, were associated with worsening outcomes. Similarly, IL-1 inhibitors like anakinra and canakinumab have shown potential in reducing inflammation and improving exercise capacity in selected patients, but these findings are not consistent across studies, and their long-term benefits in HF remain uncertain. Colchicine, a long-standing anti-inflammatory medication, has also been evaluated for its potential role in HF treatment. Although it has demonstrated some anti-inflammatory effects in cardiovascular diseases, its application in HF requires further investigation to clarify efficacy and safety. These mixed outcomes underscore the necessity for a more nuanced understanding of patient subgroups that might benefit from such therapies, as well as the timing and dosing of these interventions. Iron deficiency, a common comorbidity in HF and a contributor to inflammatory activation, represents another area of uncertainty. Intravenous iron therapies have shown promise in improving symptoms, quality of life, and even hospitalizations in HF patients. However, questions remain regarding the long-term impact of iron repletion on mortality and its role in modulating inflammatory pathways.

From a future perspective, several promising avenues warrant exploration. Advances in precision medicine could enable the identification of HF subtypes driven primarily by inflammatory mechanisms, allowing for more targeted therapeutic approaches. Biomarkers such as hs-CRP and MPO might help stratify patients who are most likely to respond to anti-inflammatory treatments. Novel therapies, including small-molecule inhibitors and biologics targeting specific inflammatory pathways, are also in development. For instance, MPO inhibitors like AZD4831 and newer IL-1β blockers are being evaluated in clinical trials and could expand the therapeutic arsenal for HF

management. Furthermore, lifestyle interventions such as structured exercise programs and dietary modifications, which have shown anti-inflammatory benefits, hold promise as adjunctive therapies. The integration of these strategies with pharmacological treatments may offer synergistic benefits. However, rigorous trials are needed to establish optimal protocols, including the type, intensity, and duration of exercise, as well as dietary patterns that most effectively reduce inflammation in HF patients.

Conclusion

HF remains one of the most pressing global health challenges, significantly affecting patients, healthcare professionals, and health systems. With its high prevalence, morbidity, and mortality rates, HF imposes a profound burden on both individuals and society. This multifaceted condition demands ongoing research and innovative therapeutic strategies to improve outcomes and quality of life for those affected. Among the various pathophysiological mechanisms implicated in HF, inflammation has emerged as a critical component, highlighting its role not only in HF but in numerous other chronic diseases.

Inflammation is an essential and vital biological response. However, when dysregulated, it can contribute to the development and progression of chronic conditions, including HF. Evidence shows that inflammatory pathways are intricately involved in cardiac remodelling, mitochondrial dysfunction, oxidative stress, and the disruption of calcium homeostasis, all of which are central to HF pathophysiology. Despite the significant progress in understanding these processes, inflammation in HF remains an area of uncertainty. The precise mechanisms by which inflammatory responses contribute to HF and the identification of effective therapeutic targets are topics of intense scientific interest but are not yet fully understood or addressed.

In recent years, the focus on inflammation in HF has intensified, leading to the development of innovative approaches and numerous clinical trials. These studies aim to unravel the complex interplay between inflammation and HF, exploring novel biomarkers for diagnosis, prognosis, and risk stratification, as well as therapeutic interventions targeting inflammatory pathways. While some promising results have been observed,

many challenges remain. The heterogeneity of HF—manifesting differently across patients with HFrEF and HFpEF—complicates the development of standardized treatment strategies, emphasizing the need for personalized approaches.

An essential aspect of managing HF is recognizing that each patient is unique, with specific clinical presentations, comorbidities, and responses to therapy. This individuality underscores the importance of a tailored approach in treatment planning. Therapies targeting inflammation or other mechanisms should be individualized, ensuring that interventions are not only effective but also safe and aligned with the patient's needs and preferences. Healthcare professionals must maintain a holistic perspective, addressing not only the physiological aspects of HF but also the emotional and social dimensions of the disease.

As we continue to deepen our understanding of HF and inflammation, it is imperative to translate emerging knowledge into clinical practice. The ongoing trials and research efforts hold the promise of unveiling new therapeutic possibilities, improving patient outcomes, and ultimately reducing the global burden of HF. However, achieving these goals requires a collaborative, multidisciplinary approach, combining the expertise of clinicians, researchers, and healthcare providers. By embracing innovation and placing the patient at the center of care, we can strive toward a future where HF management is more effective, comprehensive, and compassionate.

References

1. 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. 2022;145(18):e895-e1032.
2. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017;3(1):7-11.
3. Boulet J, Sridhar VS, Bouabdallaoui N, Tardif JC, White M. Inflammation in heart failure: pathophysiology and therapeutic strategies. Inflamm Res. 2024;73(5):709-23.
4. Narayan SI, Terre GV, Amin R, Shanghavi KV, Chandrashekar G, Ghouse F, et al. The Pathophysiology and New Advancements in the Pharmacologic and Exercise-Based Management of Heart Failure With Reduced Ejection Fraction: A Narrative Review. Cureus. 2023;15(9):e45719.
5. Ma C, Luo H, Fan L, Liu X, Gao C. Heart failure with preserved ejection fraction: an update on pathophysiology, diagnosis, treatment, and prognosis. Braz J Med Biol Res. 2020;53(7):e9646.
6. Maryam, Varghese TP, B T. Unraveling the complex pathophysiology of heart failure: insights into the role of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). Curr Probl Cardiol. 2024;49(4):102411.
7. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol. 2009;54(19):1747-62.
8. Dick SA, Epelman S. Chronic Heart Failure and Inflammation: What Do We Really Know? Circ Res. 2016;119(1):159-76.
9. Pugliese NR, Pellicori P, Filidei F, De Biase N, Maffia P, Guzik TJ, et al. Inflammatory pathways in heart failure with preserved left ventricular ejection fraction: implications for future interventions. Cardiovasc Res. 2023;118(18):3536-55.
10. Ravindran S, Rau CD. The multifaceted role of mitochondria in cardiac function: insights and approaches. Cell Commun Signal. 2024;22(1):525.
11. Nan J, Zhu W, Rahman MS, Liu M, Li D, Su S, et al. Molecular regulation of mitochondrial dynamics in cardiac disease. Biochim Biophys Acta Mol Cell Res. 2017;1864(7):1260-73.
12. Johnson E, Albakri JS, Allemailem KS, Sultan A, Alwanian WM, Alrumaihi F, et al. Mitochondrial dysfunction and calcium homeostasis in heart failure: Exploring the interplay between oxidative stress and cardiac remodeling for future therapeutic innovations. Curr Probl Cardiol. 2024;50(3):102968.
13. Dey S, DeMazumder D, Sidor A, Foster DB, O'Rourke B. Mitochondrial ROS Drive Sudden Cardiac Death and Chronic Proteome Remodeling in Heart Failure. Circ Res. 2018;123(3):356-71.
14. Tromp J, Khan MAF, Mentz RJ, O'Connor CM, Metra M, Dittrich HC, et al. Biomarker Profiles of Acute Heart Failure Patients With a Mid-Range Ejection Fraction. JACC Heart Fail. 2017;5(7):507-17.
15. Sun H, Koike T, Ichikawa T, Hatakeyama K, Shiomi M, Zhang B, et al. C-reactive protein in atherosclerotic lesions: its origin and pathophysiological significance. Am J Pathol. 2005;167(4):1139-48.
16. Pellicori P, Zhang J, Cuthbert J, Urbinati A, Shah P, Kazmi S, et al. High-sensitivity C-reactive protein in chronic heart failure: patient characteristics, phenotypes, and mode of death. Cardiovasc Res. 2020;116(1):91-100.
17. Muiesan ML, Agabiti-Rosei C, Paini A, Salvetti M. Uric Acid and Cardiovascular Disease: An Update. Eur Cardiol. 2016;11(1):54-9.

18. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003;107(15):1991-7.
19. Curran FM, Bhalraam U, Mohan M, Singh JS, Anker SD, Dickstein K, et al. Neutrophil-to-lymphocyte ratio and outcomes in patients with new-onset or worsening heart failure with reduced and preserved ejection fraction. ESC Heart Fail. 2021;8(4):3168-79.
20. Gijsberts CM, Ellenbroek G, Ten Berg MJ, Huisman A, van Solinge WW, Lam CS, et al. Effect of Monocyte-to-Lymphocyte Ratio on Heart Failure Characteristics and Hospitalizations in a Coronary Angiography Cohort. Am J Cardiol. 2017;120(6):911-6.
21. Zhang B, Li Y, Peng A, Liu C, Lin J, Feng Y, et al. Association between the pan-immune-inflammation value and coronary collateral circulation in chronic total coronary occlusive patients. BMC Cardiovasc Disord. 2024;24(1):458.
22. Inan D, Erdogan A, Pay L, Genc D, Demirtola AI, Yildiz U, et al. The prognostic impact of inflammation in patients with decompensated acute heart failure, as assessed using the pan-immune inflammation value (PIV). Scand J Clin Lab Invest. 2023;83(6):371-8.
23. Wang C, Yan W, Ren M, Zhong L. Screening significance of systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) in coronary heart disease of symptomatic youth. Immun Inflamm Dis. 2024;12(8):e1369.
24. Lai W, Zhao X, Gao Z, Huang H, Huang D, Zhou Y, et al. Association of Systemic Inflammation Level on Admission with Total and Cardiovascular-Specific Death in Heart Failure with Preserved Ejection Fraction: A Large Multi-Center Retrospective Longitudinal Study. J Inflamm Res. 2024;17:5533-42.
25. Wang M, Murdoch CE, Brewer AC, Ivetic A, Evans P, Shah AM, et al. Endothelial NADPH oxidase 4 protects against angiotensin II-induced cardiac fibrosis and inflammation. ESC Heart Fail. 2021;8(2):1427-37.
26. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/Angiotensin 1-7 Axis of the Renin-Angiotensin System in Heart Failure. Circ Res. 2016;118(8):1313-26.
27. Wang K, Basu R, Poglitsch M, Bakal JA, Oudit GY. Elevated Angiotensin 1-7/Angiotensin II Ratio Predicts Favorable Outcomes in Patients With Heart Failure. Circ Heart Fail. 2020;13(7):e006939.
28. Gupta DK, Wang TJ. Natriuretic Peptides and Cardiometabolic Health. Circ J. 2015;79(8):1647-55.
29. Fish-Trotter H, Ferguson JF, Patel N, Arora P, Allen NB, Bachmann KN, et al. Inflammation and Circulating Natriuretic Peptide Levels. Circ Heart Fail. 2020;13(7):e006570.
30. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation. 2001;103(16):2055-9.
31. Everett BM, Siddiqi HK. Heart Failure, the Inflammasome, and Interleukin-1beta: Prognostic and Therapeutic? J Am Coll Cardiol. 2019;73(9):1026-8.
32. Markousis-Mavrogenis G, Tromp J, Ouwerkerk W, Devalaraja M, Anker SD, Cleland JG, et al. The clinical significance of interleukin-6 in heart failure: results from the BIOSTAT-CHF study. Eur J Heart Fail. 2019;21(8):965-73.
33. Dimitropoulos S, Mystakidi VC, Oikonomou E, Siasos G, Tsigkou V, Athanasiou D, et al. Association of Soluble Suppression of Tumorigenesis-2 (ST2) with Endothelial Function in Patients with Ischemic Heart Failure. Int J Mol Sci. 2020;21(24).
34. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017;33(11):1342-433.
35. Aimo A, Januzzi JL, Jr., Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, et al. Clinical and Prognostic Significance of sST2 in Heart Failure: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;74(17):2193-203.
36. Besler C, Lang D, Urban D, Rommel KP, von Roeder M, Fengler K, et al. Plasma and Cardiac Galectin-3 in Patients With Heart Failure Reflects Both Inflammation and Fibrosis: Implications for Its Use as a Biomarker. Circ Heart Fail. 2017;10(3).

37. Lok DJ, Van Der Meer P, de la Porte PW, Lipsic E, Van Wijngaarden J, Hillege HL, et al. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. Clin Res Cardiol. 2010;99(5):323-8.
38. Benes J, Kotrc M, Wohlfahrt P, Conrad MJ, Franekova J, Jabor A, et al. The Role of GDF-15 in Heart Failure Patients With Chronic Kidney Disease. Can J Cardiol. 2019;35(4):462-70.
39. Wang J, Zhang T, Xu F, Gao W, Chen M, Zhu H, et al. GDF-15 at admission predicts cardiovascular death, heart failure, and bleeding outcomes in patients with CAD. ESC Heart Fail. 2023;10(5):3123-32.
40. George M, Jena A, Srivatsan V, Muthukumar R, Dhandapani VE. GDF 15--A Novel Biomarker in the Offing for Heart Failure. Curr Cardiol Rev. 2016;12(1):37-46.
41. Plonka J, Klus A, Wezyk N, Dabrowska K, Rzepiela L, Gawrylak-Dryja E, et al. Combined Use of GDF-15 and NT-Pro BNP for Outcome Prediction in Patients with Acute Heart Failure. J Clin Med. 2024;13(19).
42. Mangaonkar AA, Patnaik MM. Clonal hematopoiesis of indeterminate potential and clonal cytopenias of undetermined significance: 2023 update on clinical associations and management recommendations. Am J Hematol. 2023;98(6):951-64.
43. Yu B, Roberts MB, Raffield LM, Zekavat SM, Nguyen NQH, Biggs ML, et al. Supplemental Association of Clonal Hematopoiesis With Incident Heart Failure. J Am Coll Cardiol. 2021;78(1):42-52.
44. Dorsheimer L, Assmus B, Rasper T, Ortmann CA, Ecke A, Abou-El-Ardat K, et al. Association of Mutations Contributing to Clonal Hematopoiesis With Prognosis in Chronic Ischemic Heart Failure. JAMA Cardiol. 2019;4(1):25-33.
45. Filardi PP, Paolillo S, Indolfi C, Agostoni P, Basso C, Barilla F, et al. [Position paper of the Italian Society of Cardiology: The renin-angiotensin-aldosterone system (RAAS) blockade in heart failure patients - Part I: From RAAS identification to clinical trials]. G Ital Cardiol (Rome). 2022;23(3):217-28.
46. Tan NY, Sangaralingham LR, Sangaralingham SJ, Yao X, Shah ND, Dunlay SM. Comparative Effectiveness of Sacubitril-Valsartan Versus ACE/ARB Therapy in Heart Failure With Reduced Ejection Fraction. JACC Heart Fail. 2020;8(1):43-54.
47. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456-67.
48. Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. Stroke. 2003;34(12):2922-9.
49. Kalogeropoulos AP, Jacobs M. Improve heart function to improve heart failure outcomes: the disease-modifying effects of spironolactone. Eur J Heart Fail. 2023;25(1):114-6.
50. Keidar S, Gamliel-Lazarovich A, Kaplan M, Pavlotzky E, Hamoud S, Hayek T, et al. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. Circ Res. 2005;97(9):946-53.
51. Myhre PL, Vaduganathan M, O'Meara E, Claggett BL, de Denus S, Jarolim P, et al. Mechanistic Effects of Spironolactone on Cardiovascular and Renal Biomarkers in Heart Failure With Preserved Ejection Fraction: A TOPCAT Biorepository Study. Circ Heart Fail. 2020;13(1):e006638.
52. Joseph P, Swedberg K, Leong DP, Yusuf S. The Evolution of beta-Blockers in Coronary Artery Disease and Heart Failure (Part 1/5). J Am Coll Cardiol. 2019;74(5):672-82.
53. Arnold SV, Silverman DN, Gosch K, Nassif ME, Infeld M, Litwin S, et al. Beta-Blocker Use and Heart Failure Outcomes in Mildly Reduced and Preserved Ejection Fraction. JACC Heart Fail. 2023;11(8 Pt 1):893-900.
54. Ohtsuka T, Hamada M, Hiasa G, Sasaki O, Suzuki M, Hara Y, et al. Effect of beta-blockers on circulating levels of inflammatory and anti-inflammatory cytokines in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2001;37(2):412-7.

55. Kurum T, Tatli E, Yuksel M. Effects of carvedilol on plasma levels of pro-inflammatory cytokines in patients with ischemic and nonischemic dilated cardiomyopathy. Tex Heart Inst J. 2007;34(1):52-9.
56. Roy R, Vinjamuri S, Baskara Salian R, Hafeez N, Meenashi Sundaram D, Patel T, et al. Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors in Heart Failure: An Umbrella Review. Cureus. 2023;15(7):e42113.
57. Li C, Zhang J, Xue M, Li X, Han F, Liu X, et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. Cardiovasc Diabetol. 2019;18(1):15.
58. Bray JJH, Foster-Davies H, Stephens JW. A systematic review examining the effects of sodium-glucose cotransporter-2 inhibitors (SGLT2is) on biomarkers of inflammation and oxidative stress. Diabetes Res Clin Pract. 2020;168:108368.
59. Eid PS, Ibrahim DA, Zayan AH, Elrahman MMA, Shehata MAA, Kandil H, et al. Comparative effects of furosemide and other diuretics in the treatment of heart failure: a systematic review and combined meta-analysis of randomized controlled trials. Heart Fail Rev. 2021;26(1):127-36.
60. Sheikhi A, Jaberi Y, Esmaeilzadeh A, Khani M, Moosaeefard M, Shafaqatian M. The effect of cardiovascular drugs on pro-inflammatory cytokine secretion and natural killer activity of peripheral blood mononuclear cells of patients with chronic heart failure in vitro. Pak J Biol Sci. 2007;10(10):1580-7.
61. Satny M, Hubacek JA, Vrablik M. Statins and Inflammation. Curr Atheroscler Rep. 2021;23(12):80.
62. Park CS, Hwang IC, Park JJ, Park JH, Park JB, Cho GY. Determinants of the survival benefit associated with statins in patients with acute heart failure. ESC Heart Fail. 2021;8(6):5424-35.
63. Devaraj S, Rogers J, Jialal I. Statins and biomarkers of inflammation. Curr Atheroscler Rep. 2007;9(1):33-41.
64. Mitev V. Colchicine-The Divine Medicine against COVID-19. J Pers Med. 2024;14(7).
65. Ridker PM. From CANTOS to CIRT to COLCOT to Clinic: Will All Atherosclerosis Patients Soon Be Treated With Combination Lipid-Lowering and Inflammation-Inhibiting Agents? Circulation. 2020;141(10):787-9.
66. Bouabdallaoui N, Blondeau L, Tardif JC. Lessons from COLCOT and LoDoCo2: colchicine for secondary prevention in coronary artery disease. Eur Heart J. 2021;42(28):2800-1.
67. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383(19):1838-47.
68. Deftereos S, Giannopoulos G, Panagopoulou V, Bouras G, Raisakis K, Kossyvakis C, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Fail. 2014;2(2):131-7.
69. Hanoodi M, Mittal M. Methotrexate. StatPearls. Treasure Island (FL)2024.
70. Balanescu AR, Bojinca VC, Bojinca M, Donisan T, Balanescu SM. Cardiovascular effects of methotrexate in immune-mediated inflammatory diseases. Exp Ther Med. 2019;17(2):1024-9.
71. Gong K, Zhang Z, Sun X, Zhang X, Li A, Yan J, et al. The nonspecific anti-inflammatory therapy with methotrexate for patients with chronic heart failure. Am Heart J. 2006;151(1):62-8.
72. Pergola V, Di Salvo G, Martiniello AR, Irace L, Tedesco MA, Scialdone A, et al. [TNF alpha and heart failure]. Minerva Cardioangiol. 2000;48(12):475-84.
73. Schumacher SM, Naga Prasad SV. Tumor Necrosis Factor-alpha in Heart Failure: an Updated Review. Curr Cardiol Rep. 2018;20(11):117.
74. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation. 2004;109(13):1594-602.
75. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT, Anti TNFTACHFI. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal

antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003;107(25):3133-40.
76. Van Tassell BW, Raleigh JM, Abbate A. Targeting interleukin-1 in heart failure and inflammatory heart disease. Curr Heart Fail Rep. 2015;12(1):33-41.
77. Van Tassell BW, Arena R, Biondi-Zoccai G, Canada JM, Oddi C, Abouzaki NA, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). Am J Cardiol. 2014;113(2):321-7.
78. Van Tassell BW, Trankle CR, Canada JM, Carbone S, Buckley L, Kadariya D, et al. IL-1 Blockade in Patients With Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2018;11(8):e005036.
79. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-31.
80. Samuel M, Tardif JC. Lessons learned from large Cardiovascular Outcome Trials targeting inflammation in cardiovascular disease (CANTOS, CIRT, COLCOT and LoDoCo2). Future Cardiol. 2021;17(3):411-4.
81. Kishimoto T, Kang S, Tanaka T. IL-6: A New Era for the Treatment of Autoimmune Inflammatory Diseases. In: Nakao K, Minato N, Uemoto S, editors. Innovative Medicine: Basic Research and Development. Tokyo2015. p. 131-47.
82. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2021;397(10289):2060-9.
83. Adamstein NH, Cornel JH, Davidson M, Libby P, de Remigis A, Jensen C, et al. Association of Interleukin 6 Inhibition With Ziltivekimab and the Neutrophil-Lymphocyte Ratio: A Secondary Analysis of the RESCUE Clinical Trial. JAMA Cardiol. 2023;8(2):177-81.
84. Sinning C, Schnabel R, Peacock WF, Blankenberg S. Up-and-coming markers: myeloperoxidase, a novel biomarker test for heart failure and acute coronary syndrome application? Congest Heart Fail. 2008;14(4 Suppl 1):46-8.
85. Michowitz Y, Kisil S, Guzner-Gur H, Rubinstein A, Wexler D, Sheps D, et al. Usefulness of serum myeloperoxidase in prediction of mortality in patients with severe heart failure. Isr Med Assoc J. 2008;10(12):884-8.
86. Inghardt T, Antonsson T, Ericsson C, Hovdal D, Johannesson P, Johansson C, et al. Discovery of AZD4831, a Mechanism-Based Irreversible Inhibitor of Myeloperoxidase, As a Potential Treatment for Heart Failure with Preserved Ejection Fraction. J Med Chem. 2022;65(17):11485-96.
87. Lam CSP, Lund LH, Shah SJ, Voors AA, Erlinge D, Saraste A, et al. Myeloperoxidase Inhibition in Heart Failure With Preserved or Mildly Reduced Ejection Fraction: SATELLITE Trial Results. J Card Fail. 2024;30(1):104-10.
88. Lund LH, Lam CSP, Pizzato PE, Gabrielsen A, Michaelsson E, Nelander K, et al. Rationale and design of ENDEAVOR: A sequential phase 2b-3 randomized clinical trial to evaluate the effect of myeloperoxidase inhibition on symptoms and exercise capacity in heart failure with preserved or mildly reduced ejection fraction. Eur J Heart Fail. 2023;25(9):1696-707.
89. Morgan BP, Muci A, Lu PP, Qian X, Tochimoto T, Smith WW, et al. Discovery of omecamtiv mecarbil the first, selective, small molecule activator of cardiac Myosin. ACS Med Chem Lett. 2010;1(9):472-7.
90. Teerlink JR, Felker GM, McMurray JJV, Ponikowski P, Metra M, Filippatos GS, et al. Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure: The ATOMIC-AHF Study. J Am Coll Cardiol. 2016;67(12):1444-55.
91. Felker GM, Solomon SD, McMurray JJV, Cleland JGF, Abbasi SA, Malik FI, et al. Effects of Omecamtiv Mecarbil on Symptoms and Health-Related Quality of Life in Patients With Chronic Heart Failure: Results From the COSMIC-HF Study. Circ Heart Fail. 2020;13(12):e007814.

92. Nayor M, Houstis NE, Namasivayam M, Rouvina J, Hardin C, Shah RV, et al. Impaired Exercise Tolerance in Heart Failure With Preserved Ejection Fraction: Quantification of Multiorgan System Reserve Capacity. JACC Heart Fail. 2020;8(8):605-17.
93. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. Clin Chim Acta. 2010;411(11-12):785-93.
94. Smart NA, Steele M. The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review. Congest Heart Fail. 2011;17(3):110-4.
95. Schiattarella GG, Sannino A, Toscano E, Giugliano G, Gargiulo G, Franzone A, et al. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. Eur Heart J. 2017;38(39):2948-56.
96. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron Deficiency in Heart Failure: An Overview. JACC Heart Fail. 2019;7(1):36-46.

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ - ΚΑΡΔΙΟ-ΟΓΚΟΛΟΓΙΑ - ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ»

https://www.med.uth.gr/msc.cardio