X Reunión. Estado del Arte en
INSUFICIENCIA CARDIACA
PRÁCTICA CLÍNICA Y MODELOS ORGANIZATIVOS

Sede: Hotel Meliá María Pita, A Coruña

A CORUÑA 27-28 SEPTIEMBRE 2024

A Coruña Heart Failure Academy

X Meeting. State of the Art in
HEART FAILURE
CLINICAL PRACTICE AND ORGANIZATIONAL MODELS

Venue: Hotel Meliá María Pita, A Coruña

#ACoruñaHF2024

A CORUÑA 27-28 SEPTEMBER 2024

Iron deficiency and inflammation in HF. Update.

Clara Bonanad Lozano MD PhD

Clinical Cardiologist, Hospital Clínico Universitario de Valencia.

Department of Cardiology, Hospital Clínico Universitario de Valencia, Spain.

Associate Professor of the Department of Medicine. Faculty of Medicine and Odontology, Valencia.

Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV), Madrid

Juan Rodés Contract. Emerging Research Group

of Geriatric Cardiology, Immunothrombosis and Cardiac Rehabilitation in INSVACOR.

PI of Joint Action of the European Union Grant on Diabetes and CV Disease in INCLIVA

@BonanadClara **Web**: clarabonanad.com

SERVIZO GALEGO DE SAÚDE · ÁREA SANITARIA DA CORUÑA E CEE · inibic · SOCIEDADE GALEGA DE CARDIOLOXÍA · UNIVERSIDADE DA CORUÑA · MINISTERIO DE CIENCIA E INNOVACIÓN · Instituto de Salud Carlos III · ciber | CV · UNIÓN EUROPEA Fondo Europeo de Desarrollo Regional

Conflicts of interest

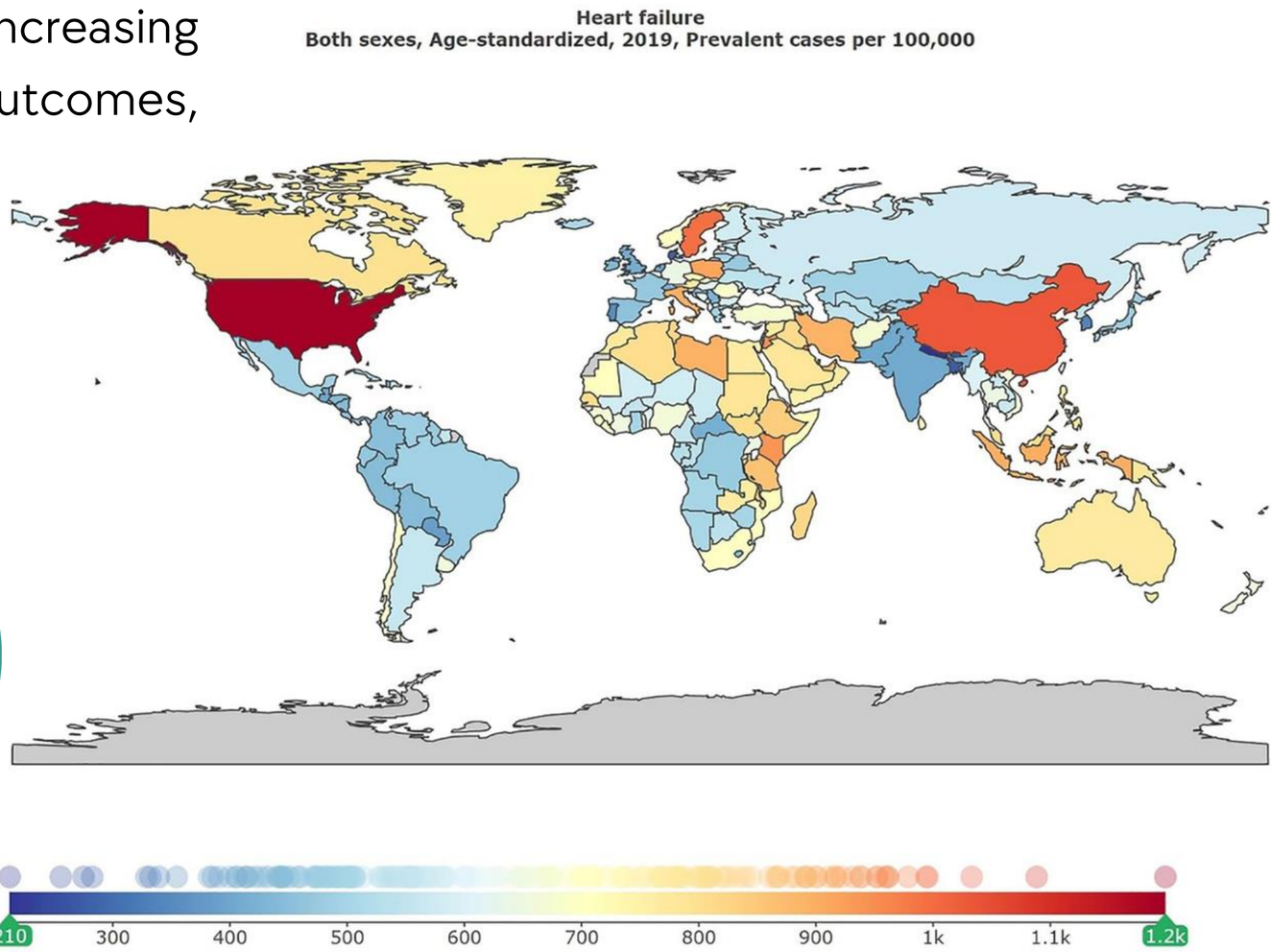
- I have received lecture fees at Pfizer/BMS, Novartis, Daiichi-Sankyo, AstraZeneca, Sanofi, Amgen, Ferrer, Boeringher-Ingelheim, Novonordisk Alter, Menarini.

- And consultancy for Daiichi-Sankyo, AstraZeneca, Sanofi, Amgen, Menarini, Pfizer/BMS, Boeringher-Ingelheim, Novonordisk.

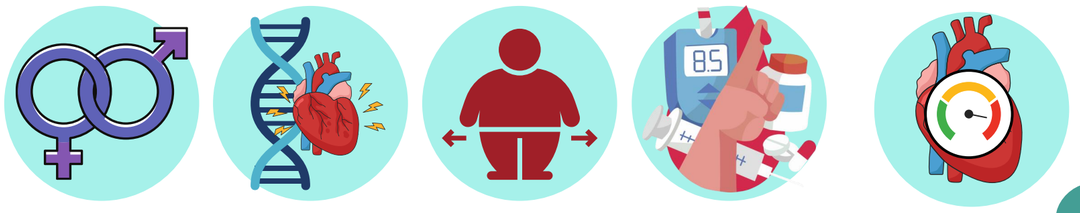
Contents

Heart failure

- Major global health concern, with its prevalence increasing due to aging populations, improved treatment outcomes, and higher survival rates



Risk Factors



But how do inflammation and iron deficiency play a role in this clinical setting?

Khan MS, et al. Nat Rev Cardiol. 2024 Jun 26.
Yan T, et al.. J Am Heart Assoc 2023;12.

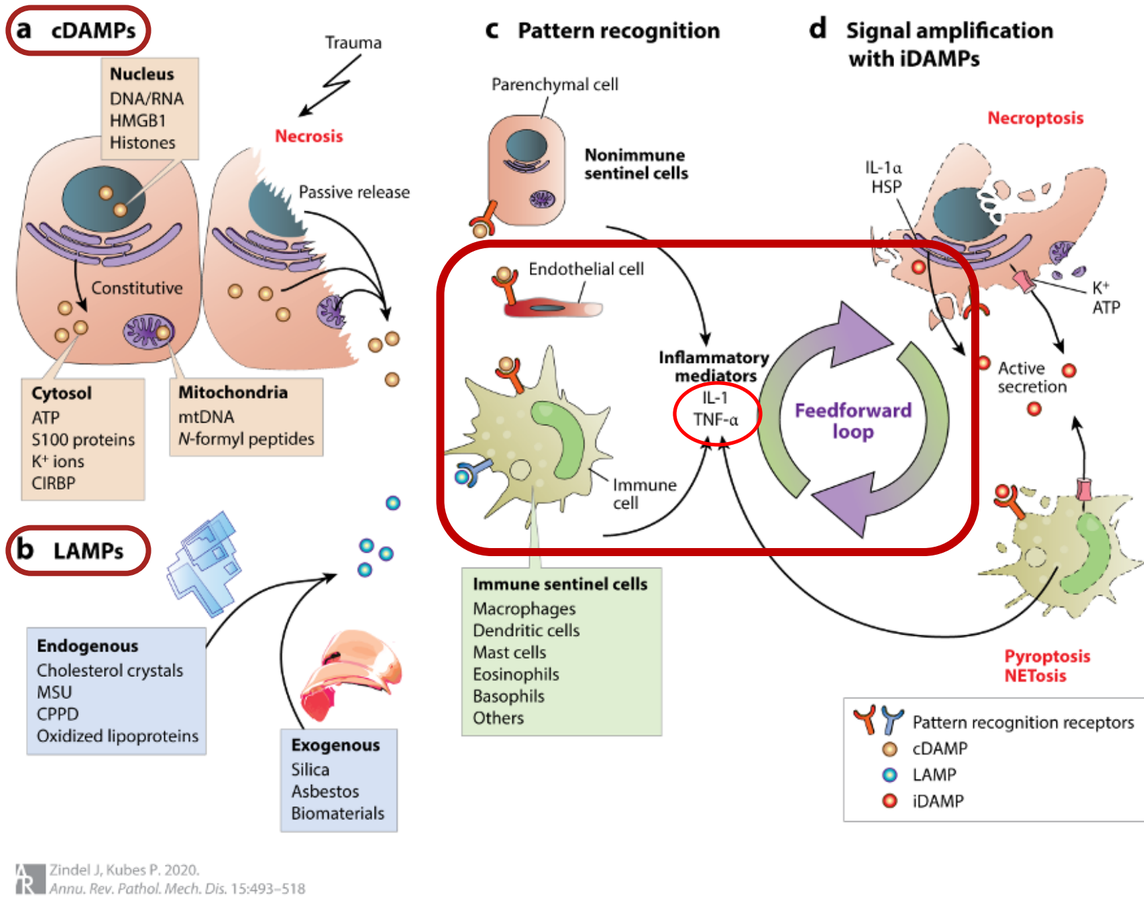
Acute vs Chronic Inflammation

	ACUTE INFLAMMATION	SYSTEMIC CHRONIC INFLAMMATION
TRIGGER	PAMPs (infection), DAMPs (cellular stress, trauma)	DAMPs ('exposome', metabolic dysfunction, tissue damage)
DURATION	Short-term	Persistent, non-resolving
MAGNITUDE	High-grade	Low-grade
OUTCOME(S	Healing, trigger removal, tissue repair	Collateral damage
AGE-RELATED	No	Yes
BIOMARKERS	IL-6, TNF-α, IL-1B, CRP	Silent-no canonical standard biomarkers

DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern

Lifestyle-associated molecular patterns (LAMPs)

Dysregulate immune response lead to unresolved inflammation, leading to chronic inflammation and immune cell-cardiac damage and related morbidity

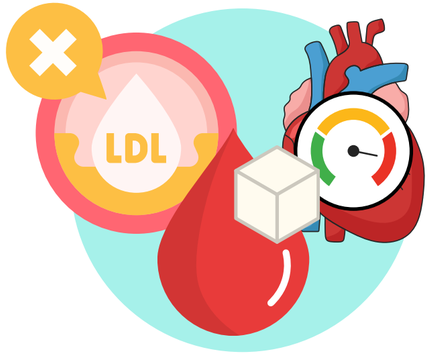


Zindel J, Kubes P. 2020. *Annu. Rev. Pathol. Mech. Dis.* 15:493–518

Khan MS, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J. Global epidemiology of heart failure. Nat Rev Cardiol. 2024 Jun 26. doi: 10.1038/s41569-024-01046-6. Epub ahead of print. PMID: 38926611.

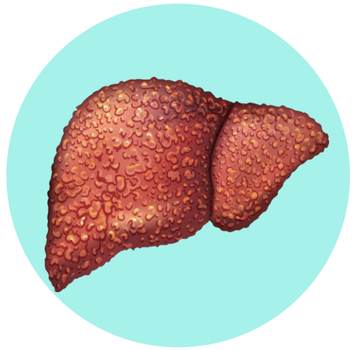
Chronic Inflammation and chronic diseases

Metabolic syndrome

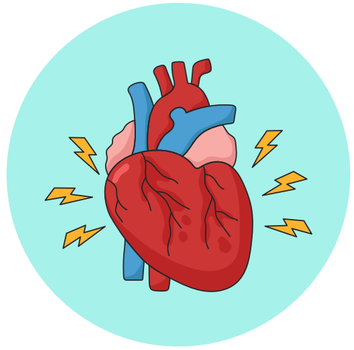


Type 2 Diabetes

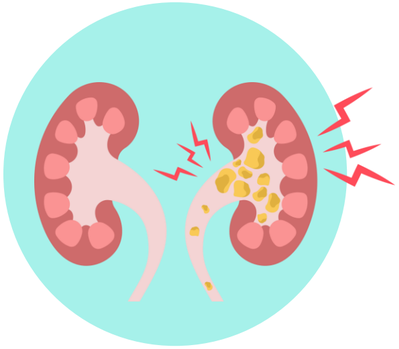
NAFLD



Cardiovascular disease



Chronic Kidney disease



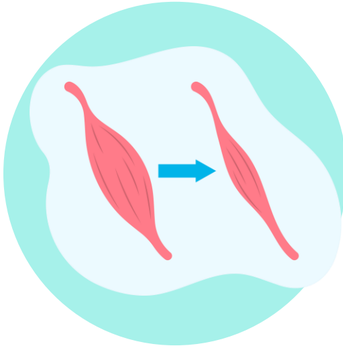
Various types of Cancer

Depression

Neurodegenerative and autoinmune diseases

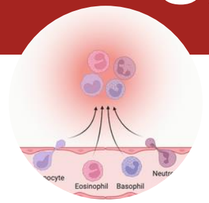
Osteoporosis

Sarcopenia



The blind spot in Cardiology

Systemic inflammation



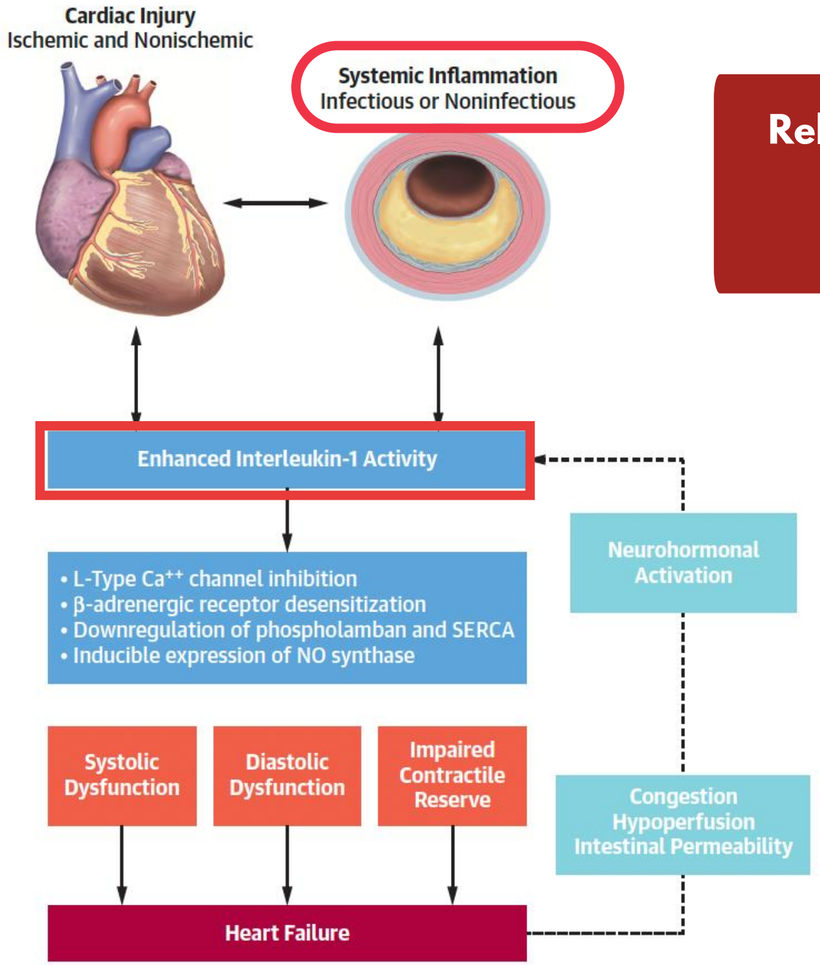
Inflamatory biomarckers Involved in Cardiovascular disorders

- HsCRP
- TNF-α
- Interleukins
- PAI-1
- NLR
- Fibrinogen

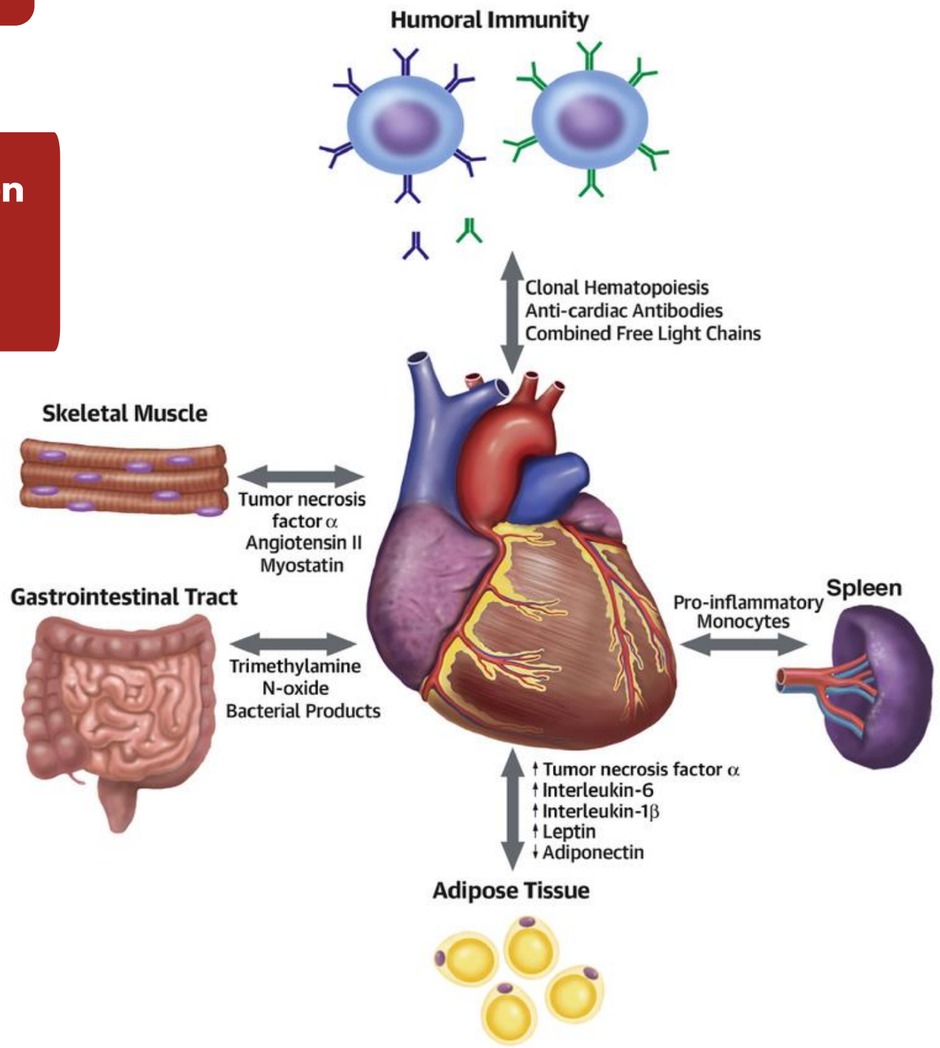
What are the inflammatory biomarkers involved in cardiovascular disorders?

Gupta, Lovish et al. “Inflammation in Cardiovascular Disease: A Comprehensive Review of Biomarkers and Therapeutic Targets.” Cureus vol. 15,9 e45483. 18 Sep. 2023, doi:10.7759/cureus.45483

The blind spot in Heart Failure



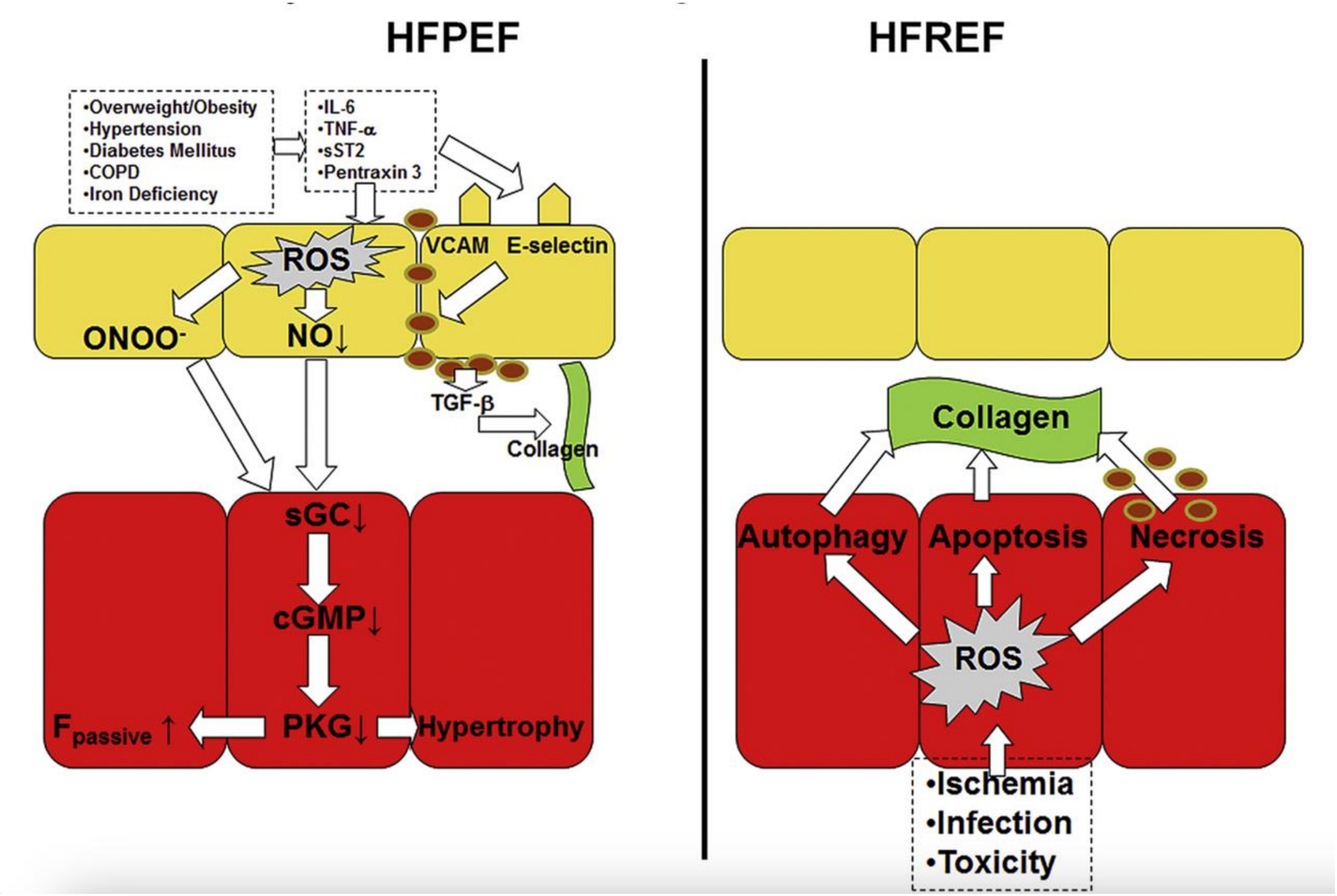
Relationship between HF and systemic inflammation



Murphy, Sean P et al. "Inflammation in Heart Failure: JACC State-of-the-Art Review." Journal of the American College of Cardiology vol. 75,11 (2020): 1324-1340. doi:10.1016/j.jacc.2020.01.014

Murphy, S.P. et al. J Am Coll Cardiol. 2020;75(11):1324-40.

Miocardial remodeling in HF



- HFpEF is associated with a proinflammatory state caused by comorbidities (obesity, DM, hypertension).

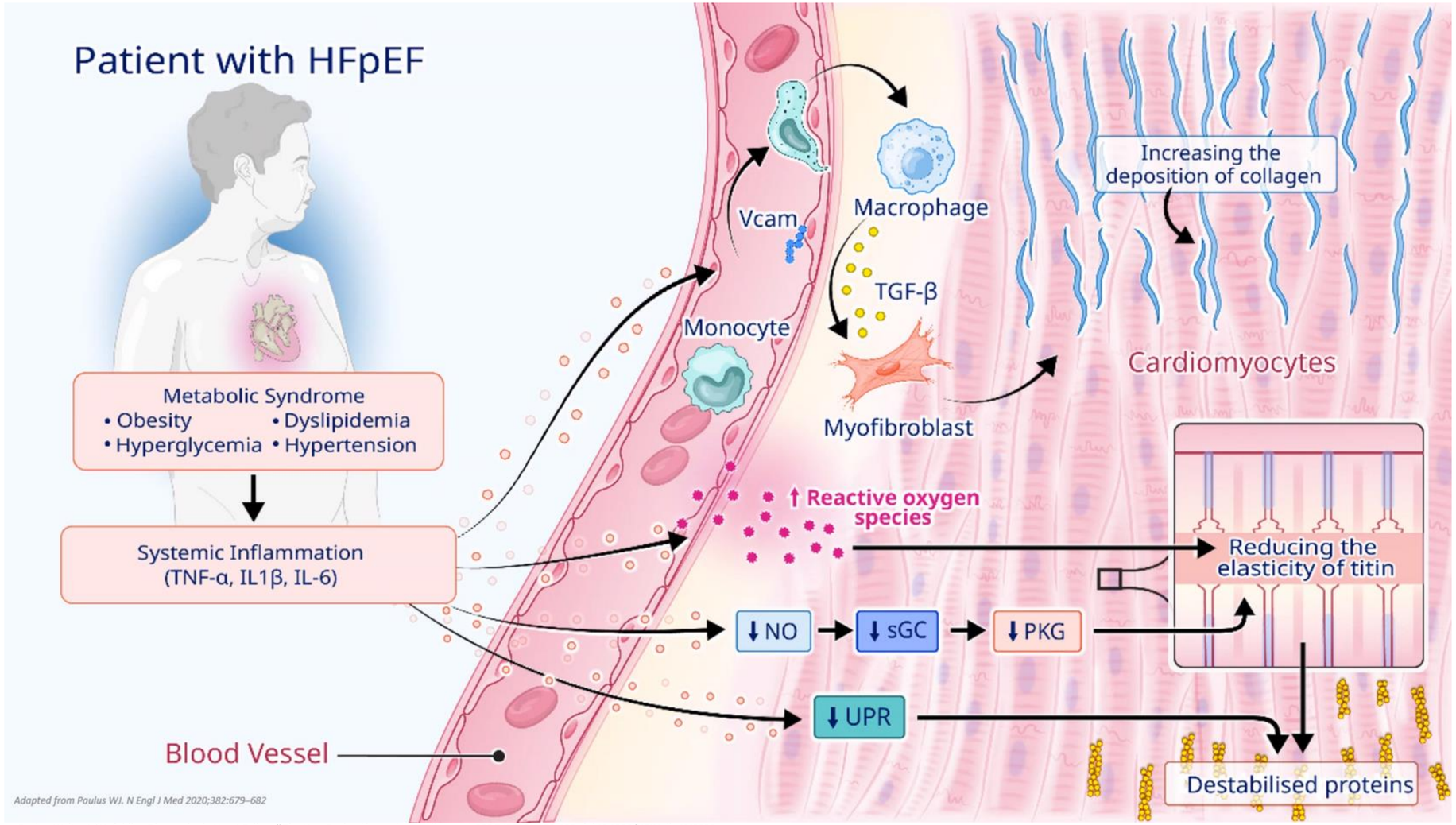
- Inflammation affects coronary microvascular endothelial cells, reducing nitric oxide and protein kinase G activity.

- Unlike HFrEF, HFpEF involves microvascular inflammation and remodeling, not cardiomyocyte loss.

- Diagnostics may include inflammatory markers and vascular responses.

Paulus, Walter J, and Carsten Tschöpe. Journal of the American College of Cardiology vol. 62,4 (2013): 263-71. doi:10.1016/j.jacc.2013.02.092

Miocardial remodeling in HF

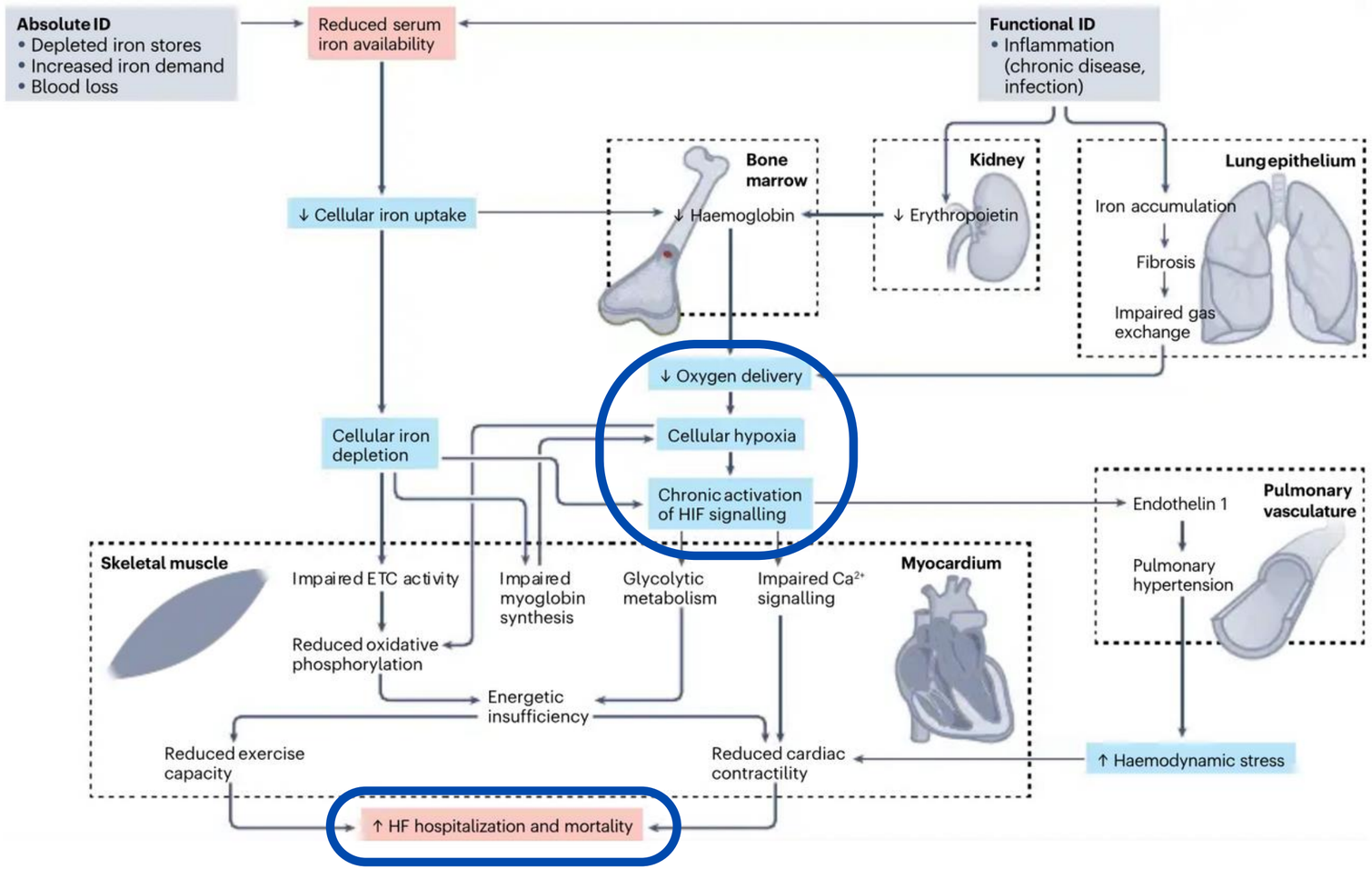


Paulus, Walter J. "Unfolding Discoveries in Heart Failure." The New England journal of medicine vol. 382,7 (2020): 679-682. doi:10.1056/NEJMcibr1913825

Iron deficiency and poor outcomes in HF

- Non-anaemic iron deficiency (NAID) is a critical focus in CV medicine due to its high prevalence, negative impact on outcomes, and role as a precursor to anemia
- In HF, iron marker variations reflect demographic factors, comorbidities, and medication effects
- NAID's adverse effects in HF may stem from unmet iron needs in the heart, muscles, and lungs, and its role in comorbidities.
- Targeting iron homeostasis and identifying tissue iron needs could revolutionize management

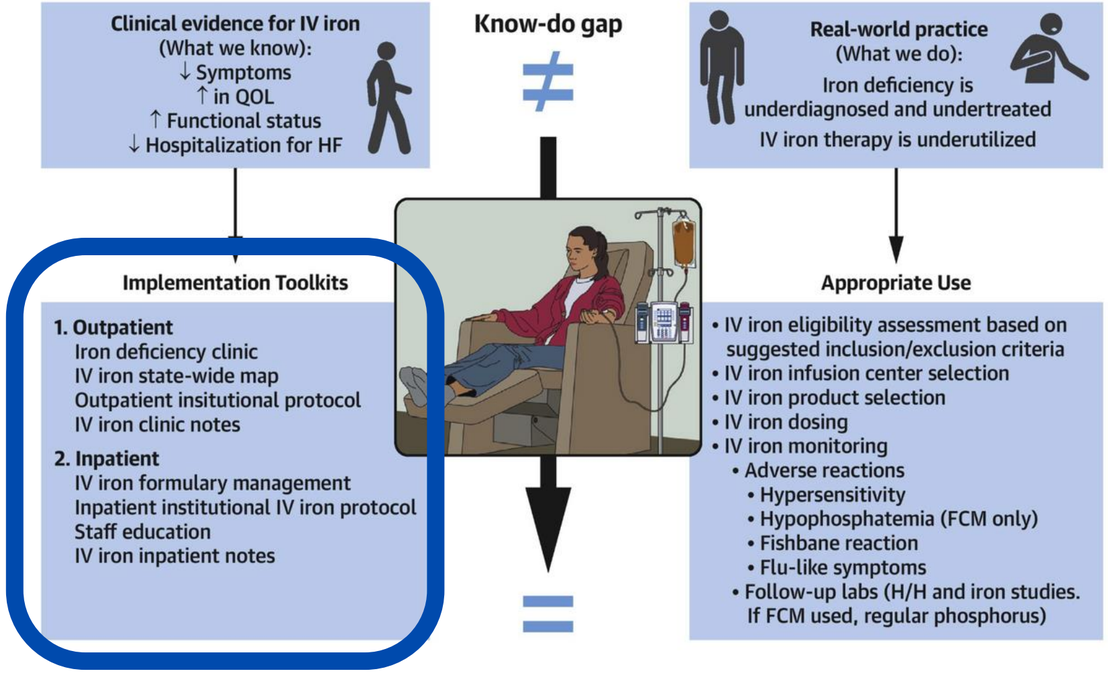
Potential mechanisms linking ID with poor outcomes in HF



Lakhal-Littleton S, Cleland JGF. Nat Rev Cardiol. **2024** Jul;21(7):463-486. doi: 10.1038/s41569-024-00988-1. Epub 2024 Feb 7. PMID: 38326440.

Iron Deficiency and Supplementation in Heart Failure: RWP

CENTRAL ILLUSTRATION: Implementation and Appropriate Use of Intravenous Iron Supplementation in Practice



Kido K, et al. J Am Coll Cardiol HF. 2024;10.1016/j.jchf.2024.05.014

-Guidelines recommend IV iron replacement in HFrEF/HFmrEF and ID based on clinical trials showing improvements in QOL exercise capacity, benefit for recurrent HF hospitalization

Recommendation Table 5 — Recommendations for the management of iron deficiency in patients with heart failure

Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] 12,41,47–49	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.[c] 12,41,43–46	IIa	A

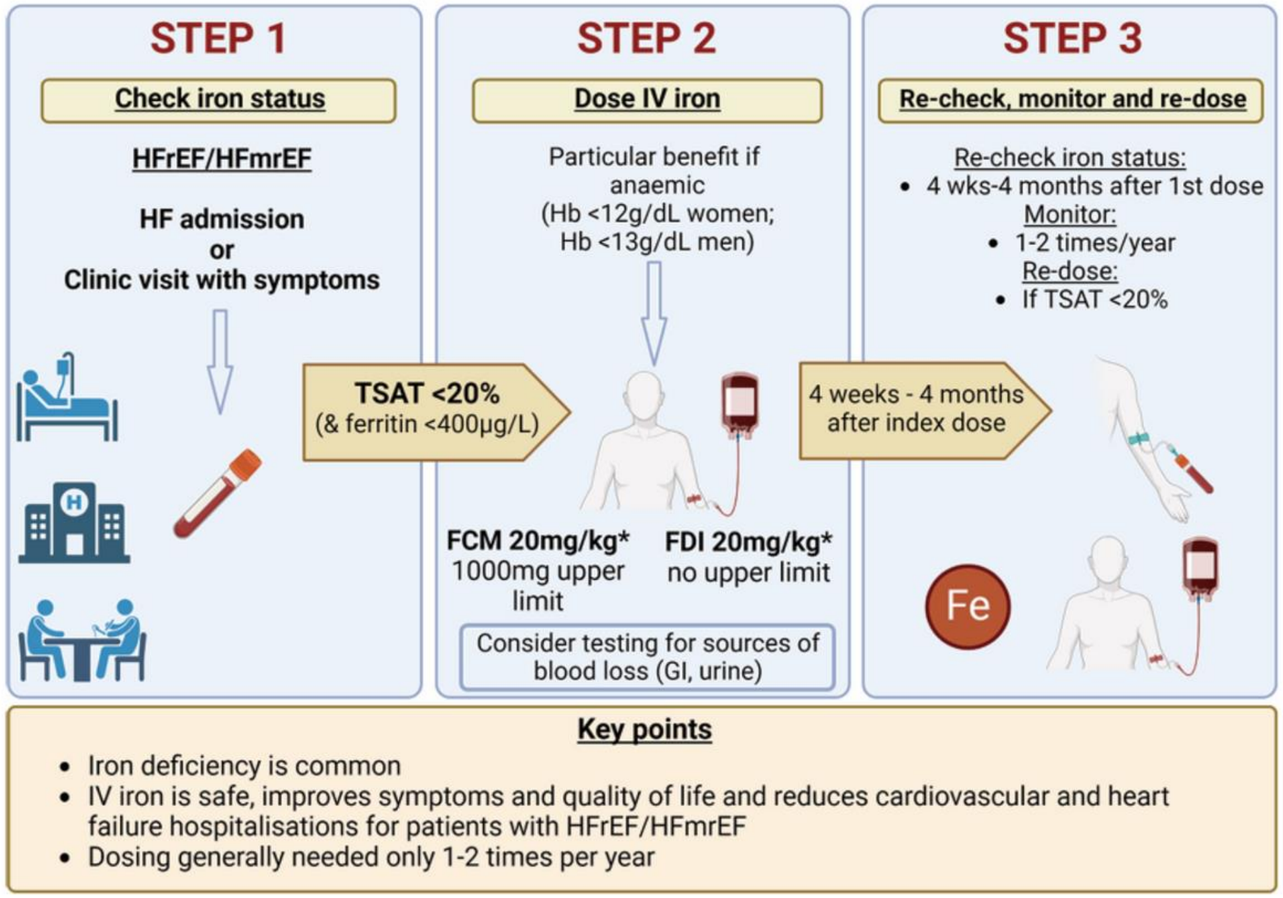
-Limited Access: Despite prevalence of ID is aprox. 50% infusion centers. are scarce in rural areas, leading to low IV iron treatment (rates 20% of eligible patients).

Kido, K, Beavers, C, Dulnuan, K. et al. J Am Coll Cardiol HF. 2024, 0 (0) .https://doi.org/10.1016/j.jchf.2024.05.014

N Engl J Med 2013;368:1210–9. Eur Heart J 2016; 37:2129–200.

Iron Deficiency and Supplementation in Heart Failure

XI Meeting. State of the Art in HEART FAILURE
CLINICAL PRACTICE AND ORGANIZATIONAL MODELS
A CORUÑA 27-28 SEPTEMBER 2024
A Coruña Heart Failure Academy



Graham, Fraser J et al. "Treating iron deficiency in patients with heart failure: what, why, when, how, where and who." *Heart (British Cardiac Society)*, heartjnl-2022-322030. 23 Aug. 2024, doi:10.1136/heartjnl-2022-322030

- Intravenous iron improves symptoms, quality of life, reduces hospitalizations, and may enhance long-term survival in HF
- The impact on cardiovascular mortality remains inconsistent, indicating the need for further research
- Ferric carboxymaltose is commonly used for its safety profile and ability to deliver high doses in a single infusion
- Regular assessment of iron status is recommended for HF patients, with TSAT <20% and low ferritin indicating ideal candidates for treatment
- Challenges include the lack of a consensus on iron deficiency definition, variable treatment practices, and safety concerns in certain subgroups

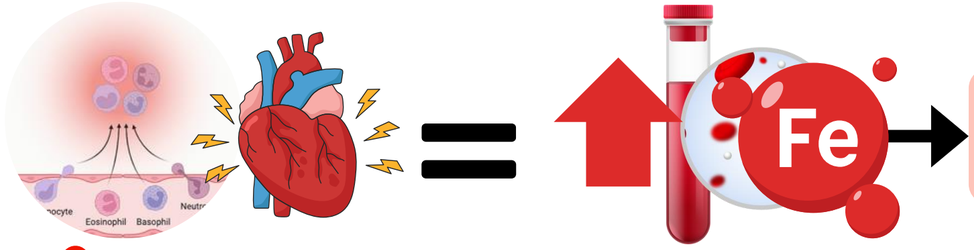
Latest insights in HF

Current definition of ID: serum ferritin <100 µg/L (regardless of TSAT) or serum ferritin level of 100 to 299 µg/L if TSAT is <20%

Serum ferritin 20–100 µg/L are considered iron deficient, even if there is no evidence of hypoferremia

Patients with TSAT ≥20% and normal ferritin (20-100 µg/L) who are not iron-deficient

Do not respond favourably to iron therapy



Patients with meaningful hypoferremia (TSAT <20%) are not considered iron deficient if the serum ferritin level is ≥300 µg/L

NEW!

The most **evidence-based definition of iron deficiency** is hypoferremia, as evidenced by a **TSAT <20%**

- Demonstrably **iron deficient on bone marrow**
- **Improvement in symptoms and functional capacity**
- **Largest reduction in the risk of cardiovascular death or HF hospitalization with IV iron therapy**

Graham FJ, Guha K, Cleland JG, Kalra PR. Managing iron deficiency in heart failure patients: aspects of treatment. **Heart. 2024** Aug 23:heartjnl-2022-322030. doi: 10.1136/heartjnl-2022-322030. Epub ahead of print. PMID: 39160066.

10.1161/CIRCULATIONAHA.124.068883

Redefining Iron Deficiency in Patients With Chronic Heart Failure

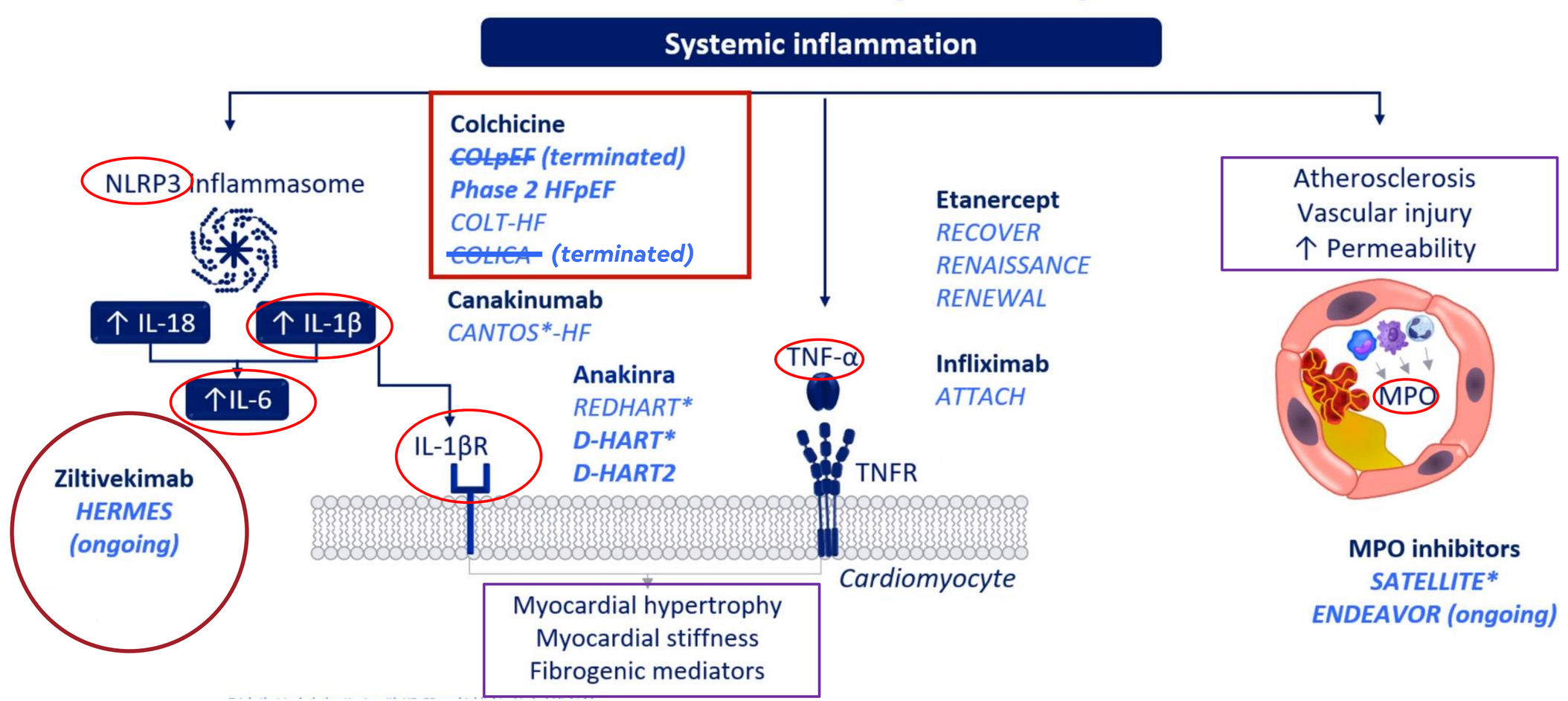
It is proposed that the current definition of ID based on ferritin in HF be abandoned, and that a definition based on hypoferremia (TSAT <20%) be adopted

Milton Packer, MD[1,2]; Stefan D. Anker, MD, PhD[3]; Javed Butler, MD, MPH, MBA[4,5];

John G. F. Cleland, MD[6]; Paul R. Kalra, MD[7,8,9]; Robert J. Mentz, MD[10];

Piotr Ponikowski, MD[11,12]; Khawaja M. Talha, MBBS[5]

Clinical trials of anti-inflammatory therapies for HF



a

Systemic Inflammation in HF: Impact of Drugs on Pathophysiology (COLICA)

n= 278 AHF
- ✓ Clinical congestion
- ✓ ≥ 40 mg i.v. furosemide
- ✓ NT-proBNP > 900pg/mL

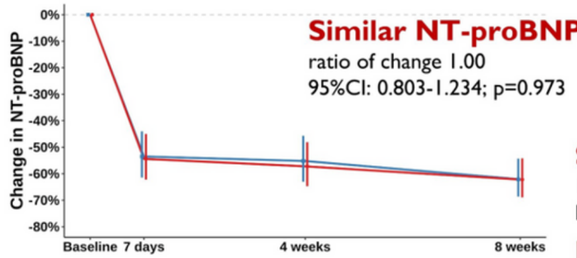
< 24 hours

Randomization
Double-blind

Colchicine N=141 | Placebo N=137

- Age median 75 years, Male 68%
- LVEF median 40%
- NT-proBNP median 4262 pg/ml
- In-hospital 57% / Out-patient 43%

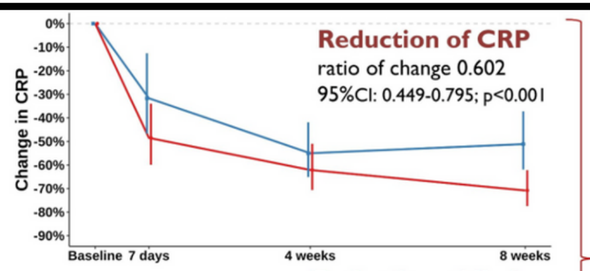
Follow-up — Efficacy and Safety of colchicine in AHF → 8 weeks



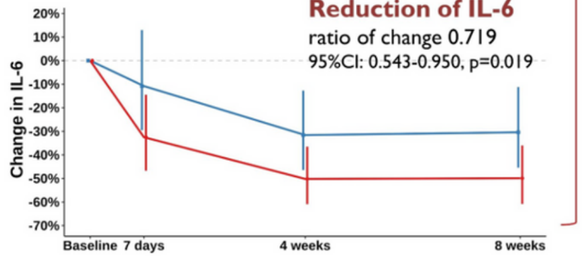
Similar NT-proBNP reduction
ratio of change 1.00
95%CI: 0.803-1.234; p=0.973

Similar WHF events
14.9% vs. 16.8%
HR 0.88 (CI95% 0.49 to 1.61)

No safety concerns



Reduction of CRP
ratio of change 0.602
95%CI: 0.449-0.795; p<0.001

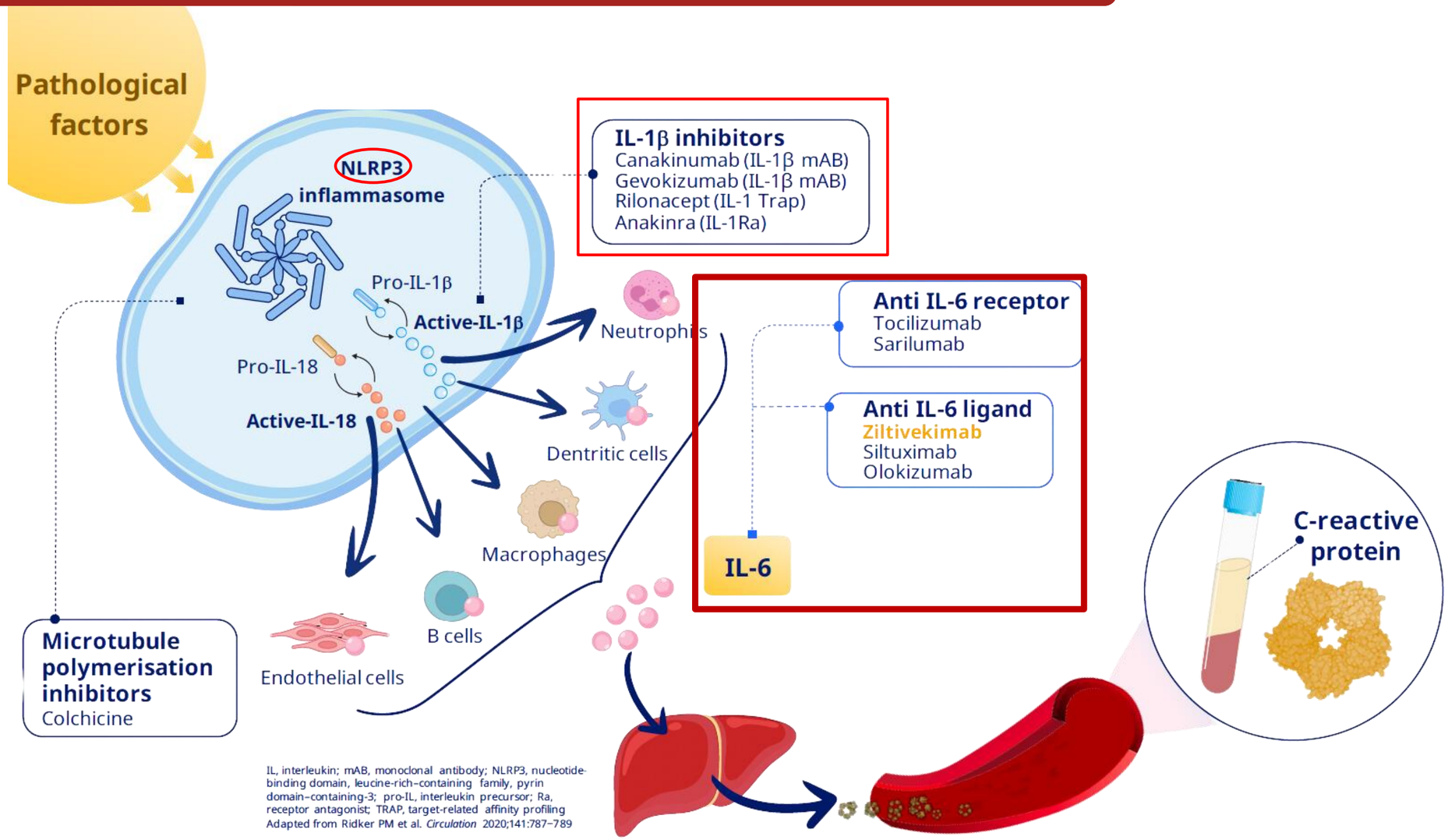


Reduction of IL-6
ratio of change 0.719
95%CI: 0.543-0.950, p=0.019

Anti-inflammatory effect

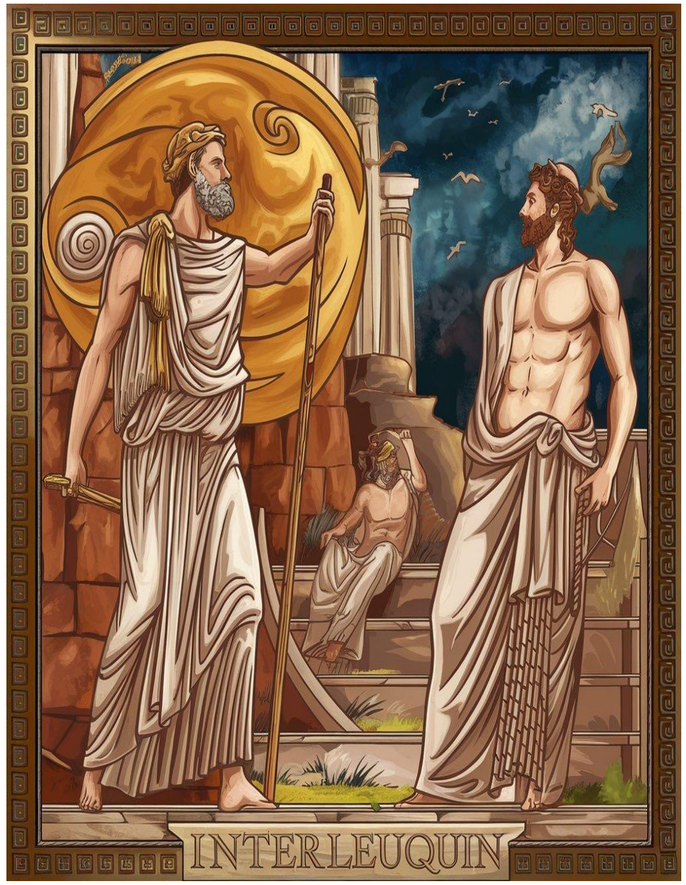
Eur Heart J, ehae538, https://doi.org/10.1093/eurheartj/ehae538

Targets IL-6 ligand



IL, interleukin; mAB, monoclonal antibody; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; pro-IL, interleukin precursor; Ra, receptor antagonist; TRAP, target-related affinity profiling
Adapted from Ridker PM et al. *Circulation* 2020;141:787–789

RESCUE Trial: Ziltivekimab significantly reduced inflammatory biomarkers vs placebo



In the randomised, double-blind, dose-setting phase 2b RESCUE trial, 264 patients with stage 3–5 CKD (eGFR >10 and <60 mL/min per 1.73 m^3) and systemic inflammation (hsCRP ≥2 mg/L) received ziltivekimab (7.5 mg, 15 mg or 30 mg s.c.) or placebo every 4 weeks for up to 24 weeks[1]

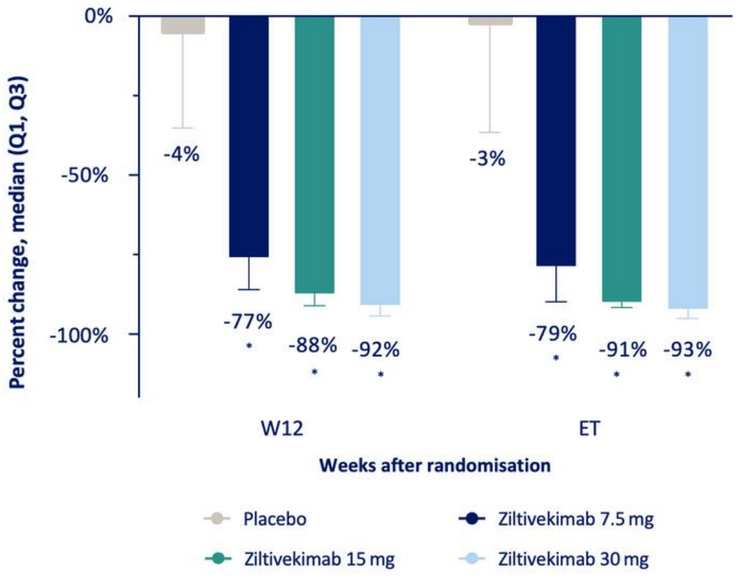
The primary endpoint was met:[1]

From baseline to week 12, ziltivekimab resulted in significant dose-dependent reductions in hsCRP (p<0.0001) compared with placebo

Key secondary/exploratory endpoints:[1]

Fibrinogen, SAA and haptoglobin levels were also reduced compared with placebo (p<0.0001 for all)

Ziltivekimab treatment for 12 weeks significantly reduced hsCRP[1,2]



No increased risk of bleeding with low rates of thrombocytopenia (0% grade 2)†

Rate of any infection was comparable to placebo

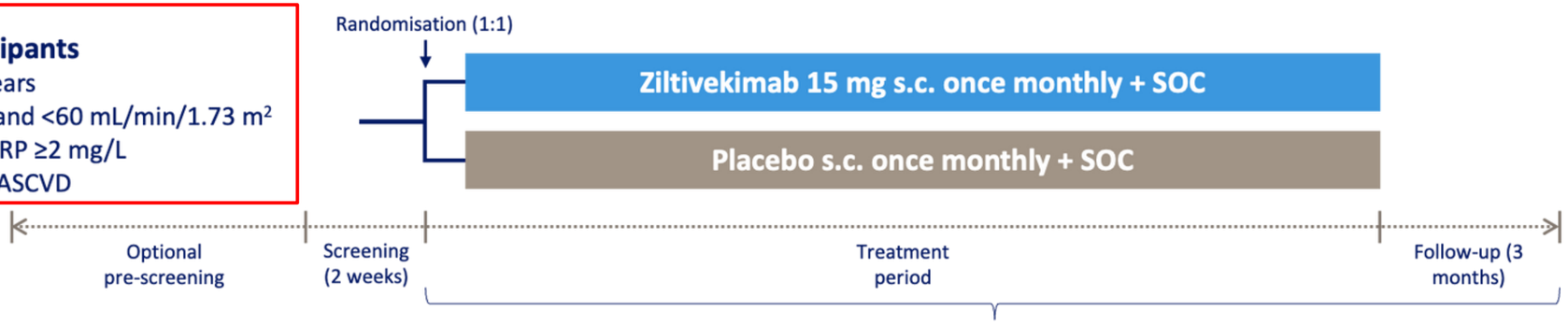
Minimal effect on liver enzyme (AST/ALT) elevations

No moderate or severe cases of neutropenia, only few cases of mild neutropenia observed (1.5% grade 2)*

*p<0.0001 vs placebo
ASCVD. Atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ET, end of treatment; hsCRP, high-sensitivity C-reactive protein; s.c., subcutaneous; Q, quartile; SAA, serum amyloid A; W12, Week 12
1. Ridker PM et al. Lancet 2021;397:2060–2069;

Ziltivekimab is also being assessed in patients with ASCVD, CKD and systemic inflammation in the ZEUS CVOT

6,200 participants
- Age ≥18 years
- eGFR ≥15 and <60 mL/min/1.73 m^2
- Serum hsCRP ≥2 mg/L
- History of ASCVD



Primary endpoint:
Time to first occurrence of 3-point MACE:
- CV death
- non-fatal MI
- non-fatal stroke

Secondary endpoints:
- Time to first occurrence of expanded MACE (CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina pectoris requiring urgent coronary revascularisation)
- Number of HHF or urgent HF visit
- Time to occurrence of all-cause mortality
- Time to first occurrence of a composite CKD endpoint*

*≥40% reduction in eGFR, death from kidney failure, onset of persistent eGFR <15 mL/min/1.73 m2 or initiation of chronic kidney replacement therapy
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcome trial; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event; MI, myocardial infarction; s.c., subcutaneous; SOC, standard of care; 1. Novo Nordisk A/S. NCT05021835. Available at: https://clinicaltrials.gov/ct2/show/NCT05021835 (accessed June 2022); 2. Novo Nordisk A/S. Data on file

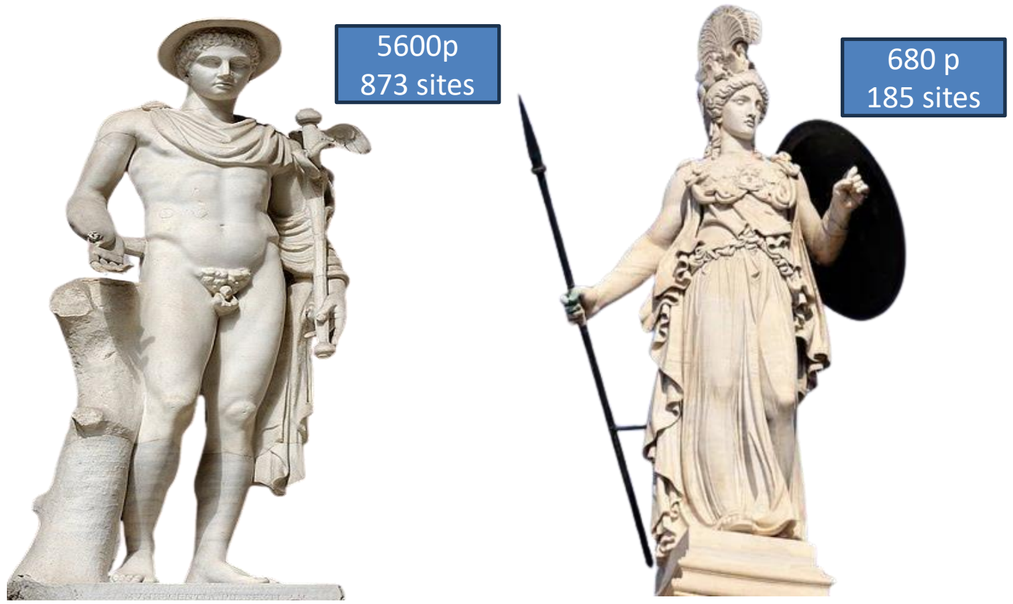
HERMES and ATHENA : HFpEF and Systemic Inflammation (ongoing)

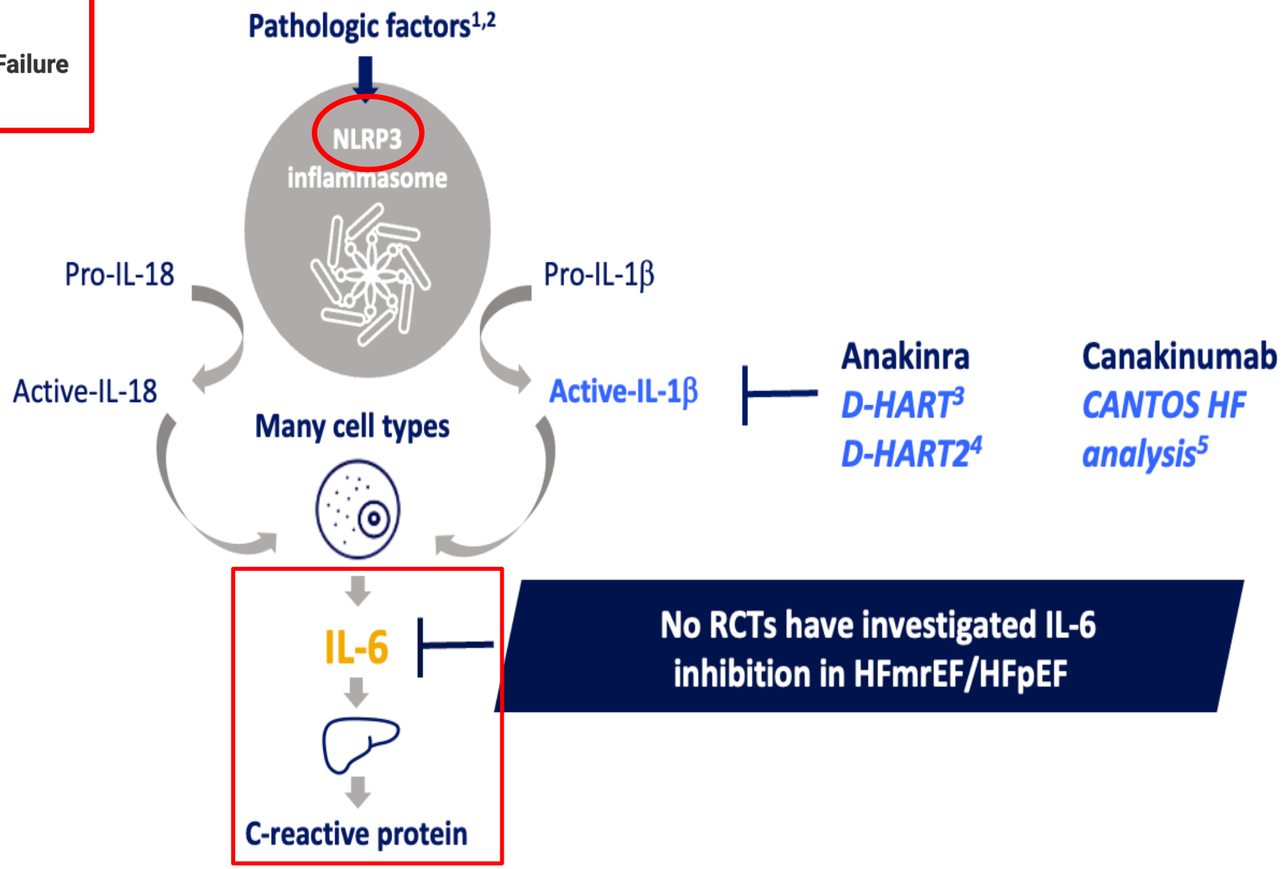
RECRUITING

A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation (HERMES)

RECRUITING

A Research Study Looking Into How Ziltivekimab Works Compared to Placebo in Participants With Heart Failure and Inflammation (ATHENA)





HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IL-18, interleukin-18; IL-1β; interleukin-1β; IL-6, interleukin 6; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3; RCT, randomised controlled trial 1. Ridker et al. Circ Res 2016;118:145–56 (Figure adapted); 2. Wu et al. Front Physiol 2021;12:709703; 3. Van Tassell et al. Am J Cardiol 2014;113(2):321–7; 4. Van Tassell et al. Am J Cardiol 2018;11:e005036; 5. Everett et al. Circulation 2019;139:1289–99

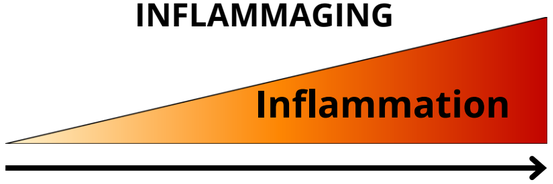
Inflammation and iron deficiency in ACS?

XI Meeting. State of the Art in HEART FAILURE
CLINICAL PRACTICE AND ORGANIZATIONAL MODELS
A CORUÑA 27-28 SEPTEMBER 2024
A Coruña Heart Failure Academy

- **Inflammation**, frailty, biological age and telomere shortening in patients after ACS are associated with worse prognosis

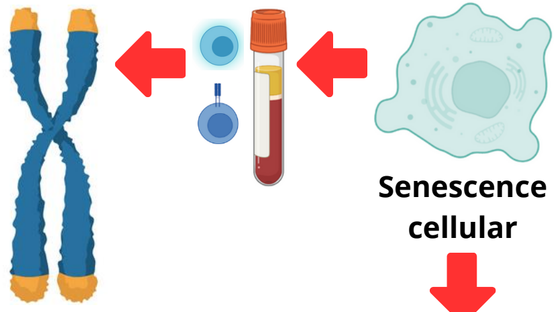
- In this study we sought to test whether these parameters differ between treated and untreated patients with **iron deficiency**.

INFLAMMAGING



- To carry out this objective, the inflammation profile and extended **ferric profile (HIF1 and hepcidin)** will be analysed using the ELISA
- In addition, telomere length will be collected and analysed with qPCR and biological age from methylation of the ELOVL2 gene

- Finally, **Klotho** and **FGF23** will be analysed

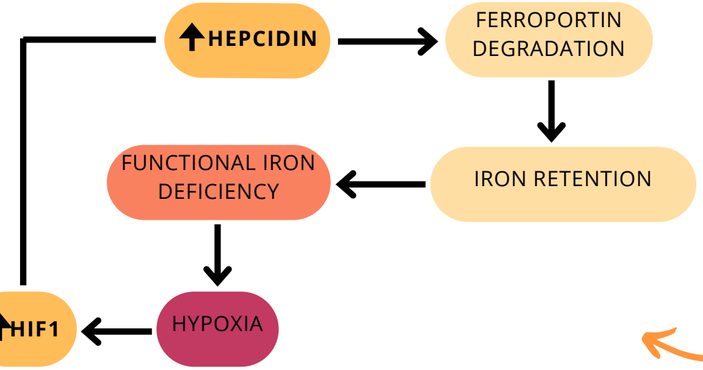


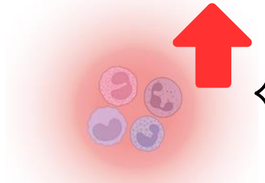
Frailty

FRAIL Criteria

FRAIL	Criteria
F	Fatigue
R	Resistence
A	Aerobic
I	Illnesses
L	Lost of Weight

¿Ferropenia?





Inflammation

- Interleukins
- PCR
- PCRus
- TNF-α

s-Klotho

Major:
- BMI
- Triglycerides
- Cholesterol
- Cardiovascular risk

FGF23

- Cardiovascular event
- Cardiac fibrosis

Key takeaways

- **LAMPs** (**lifestyle**-associated molecular patterns): molecules that the immune system cannot clear, preventing resolution of inflammation, leading to chronic inflammation and leukocyte-mediated damage

- In **HFpEF**, systemic inflammation from **comorbidities** drives myocardial dysfunction, while in **HFrEF**, remodeling results from cardiomyocyte loss.

- **Iron Deficiency affects nearly half of HF patients**, yet intravenous iron is underutilized

- Further research is needed to clarify **intravenous iron's role** in iron deficiency debates

- Promising **anti-inflammatory therapies** are underway

HENKO: "Moving forward with no turning back (hen: change, ko: a different light)."