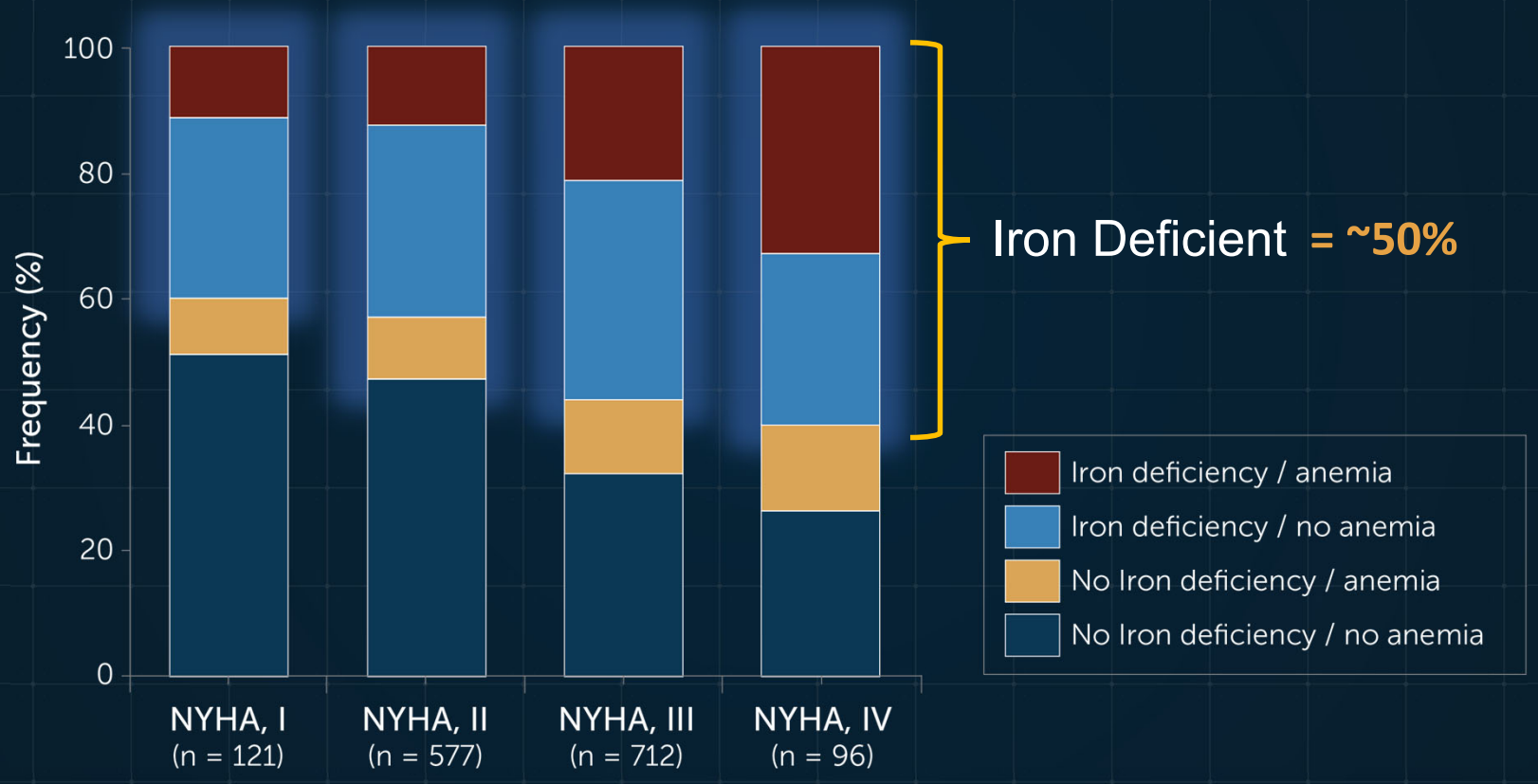
Common Misconceptions About Iron Deficiency in Heart Failure and What to Do About It

Misconception #1

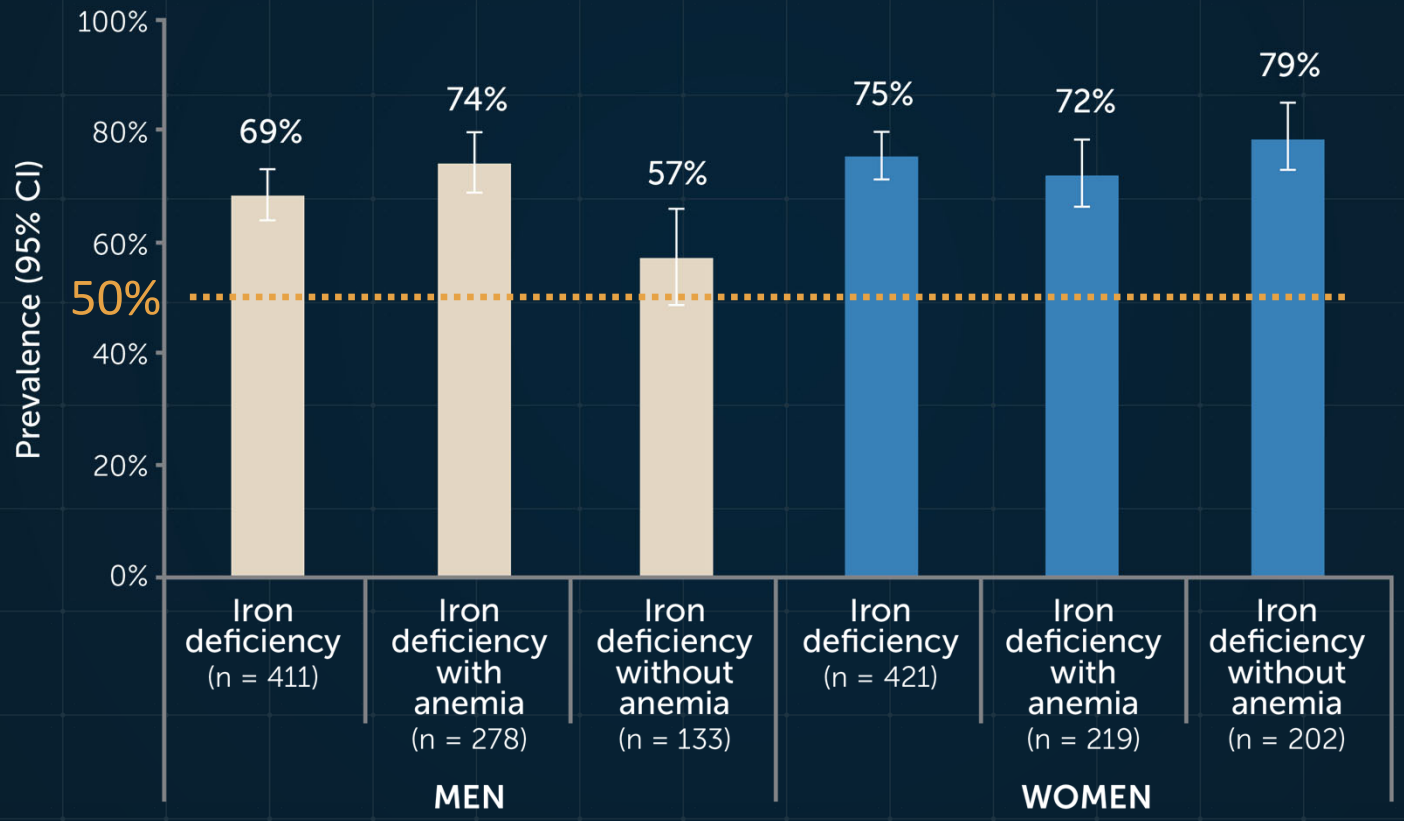
Iron deficiency is of little importance in heart failure.

Iron Deficiency: Common in All NYHA Classes



NYHA, New York Heart Association; Klip IT, et al. *Am Heart J.* 2013;165(4):575-582.

Iron Deficiency: Prevalent in Acute Heart Failure



Cohen-Solal A, et al. *Eur J Heart Fail.* 2014;16(9):984-991.

Iron Deficiency Is Common

- Associated with:
  - Poor quality of life
  - Poor functional capacity
  - Worse prognosis

Screening for Iron Deficiency Is Indicated

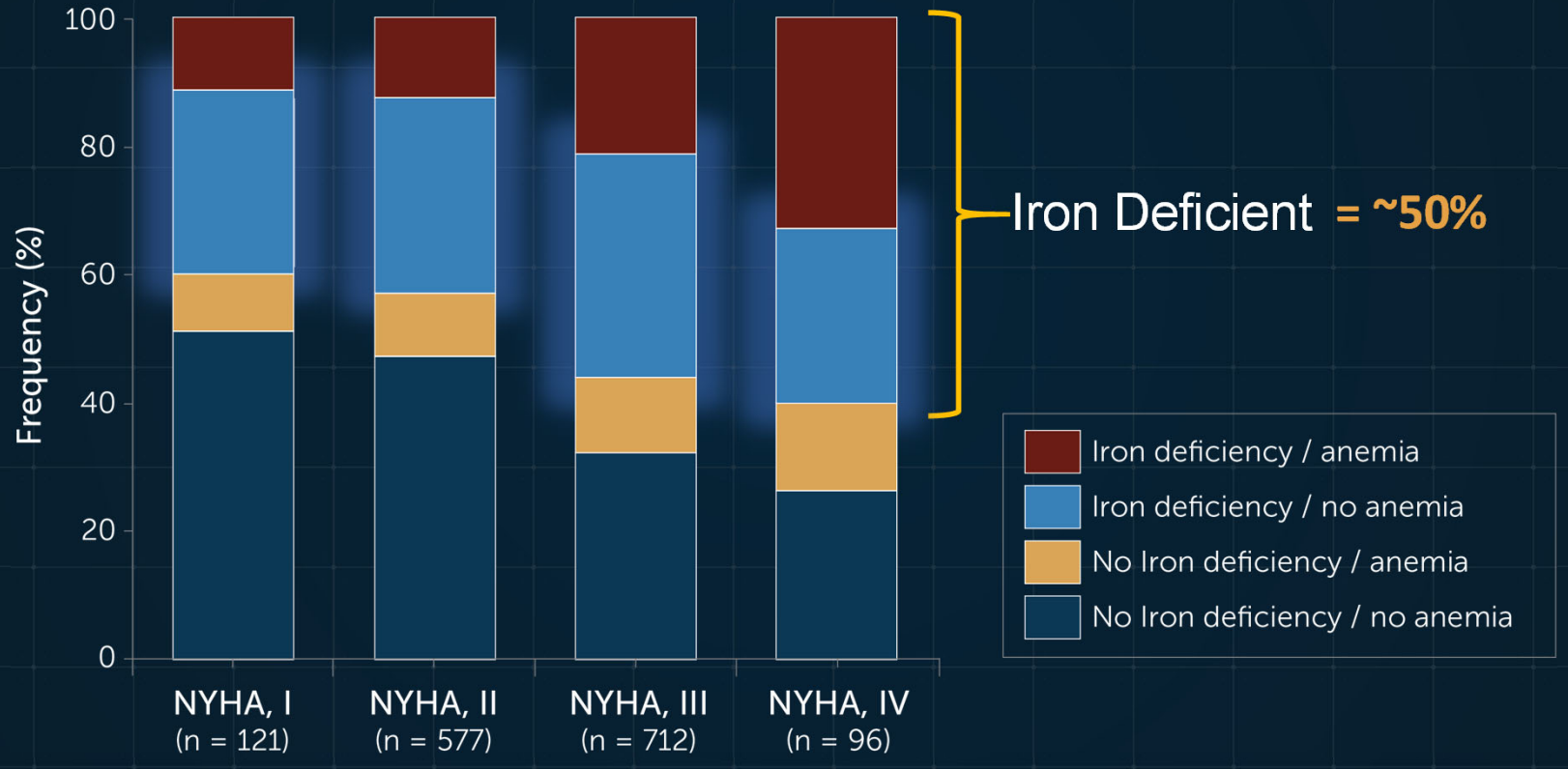
- ESC Heart Failure Guidelines
  - Ferritin and TSAT testing are recommended for newly diagnosed patients with HF (Class I, Level C)

ESC, European Society of Cardiology HF, heart failure; TSAT, transferrin saturation. Ponikowski P, et al. *Eur Heart J*. 2016;18(8):891-975.

Misconception #2

Iron deficiency is only relevant in the presence of anemia and is not a stand-alone condition.

Iron Deficiency: Common in All NYHA Classes



NYHA, New York Heart Association; Klip IT, et al. *Am Heart J.* 2013;165(4):575-582.

“Only screening for hemoglobin misses 2/3 of patients with iron deficiency.”

Large-scale Intervention Trials

- FAIR-HF
- CONFIRM-HF

Anker SD, et al. *N Engl J Med*. 2009;361(25):2436-2448.
Ponikowski P, et al. *Eur Heart J*. 2015;36(11):657-668.

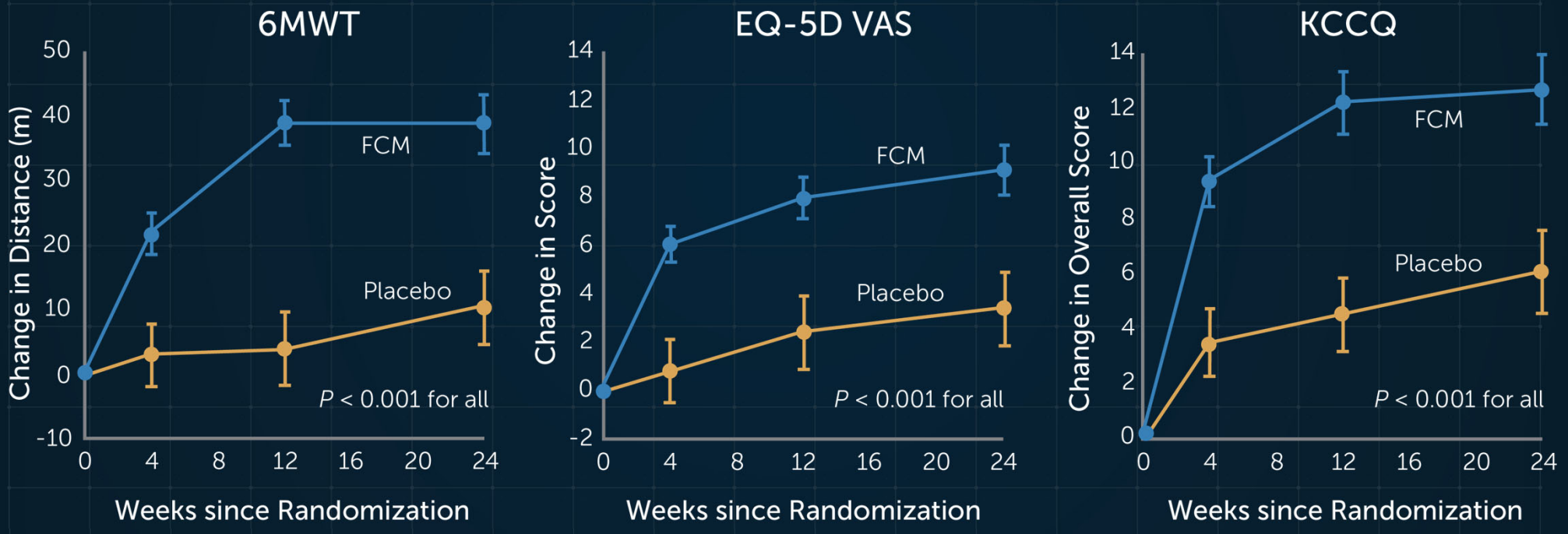
FAIR-HF

- Inclusion criteria:
- Symptomatic CHF NYHA class II or III
- LVEF (≤40% NYHA class II or ≤45% NYHA class III)
- ID (ferritin <100 µg/L or 100–299 µg/L if TSAT <20%)
- ± Anemia (Hb 9.5–13.5 g/dL)

Anker SD, et al. *N Engl J Med*. 2009;361(25):2436-2448.

FAIR-HF: IV Iron Improves 6MWT and Quality of Life

Treatment effects were similar in iron deficiency ± anemia.



6MWT, 6-minute walk test; ED-5D VAS, European Quality of Life-5 Dimensions Visual Analog Scale; FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy questionnaire. Anker SD, et al. *N Engl J Med*. 2009;361(25):2436-2448.

Misconception #3

Measuring ferritin levels is sufficient to identify iron deficiency.

Why Patients with HF Often Develop ID

Absolute Iron Deficiency (Reduced Iron Storage)

Reduced Intake

- Malnutrition
  - Poor appetite/poor intake
- Malabsorption
  - GI edema
  - Hepcidin upregulation
  - Medications
    - Proton pump inhibitors
    - Phosphate binders

Increased Loss

- GI blood losses
  - Peptic ulceration/ mucosal integrity
  - Medications
    - Aspirin
    - Anticoagulants
    - Antiplatelets
    - NSAIDs

Functional Iron Deficiency (Reduced Iron Mobilization)

Inflammation

- Cytokines, IL-6, IL-1, TNF-α
- Blunted responses to EPO
- Apoptosis of erythroid progenitors
- Hepcidin-mediated malabsorption and RES pooling

EPO, erythropoietin; HF, heart failure; ID, iron deficiency; NSAIDs, nonsteroidal anti-inflammatory drugs; RES, reticuloendothelial system.

Jankowska EA, et al. *Eur Heart J*. 2013;34(11):816-829. Wong CC, et al. *Heart Lung Circ*. 2016;25(3):209-216.

Iron Deficiency

Ferritin <100 µg/L

or

Ferritin 100–299 µg/L and TSAT <20%

Patient Case 1

- Female
- Class II heart failure
- LVEF 35%
- Hemoglobin 12 g/dL
- Ferritin 185 µg/L
- TSAT 19%

- What is your diagnosis?

Patient Case 1

- Female
- Class II heart failure
- LVEF 35%
- Hemoglobin 12 g/dL
- Ferritin 185 µg/L
- TSAT 19%

- Diagnosis:
  - Borderline anemic
  - Iron deficient

Patient Case 2

- **Male**
- Class II heart failure
- LVEF 35%
- Hemoglobin 12 g/dL
- Ferritin 185 µg/L
- TSAT 19%

- What is your diagnosis?

Anemia

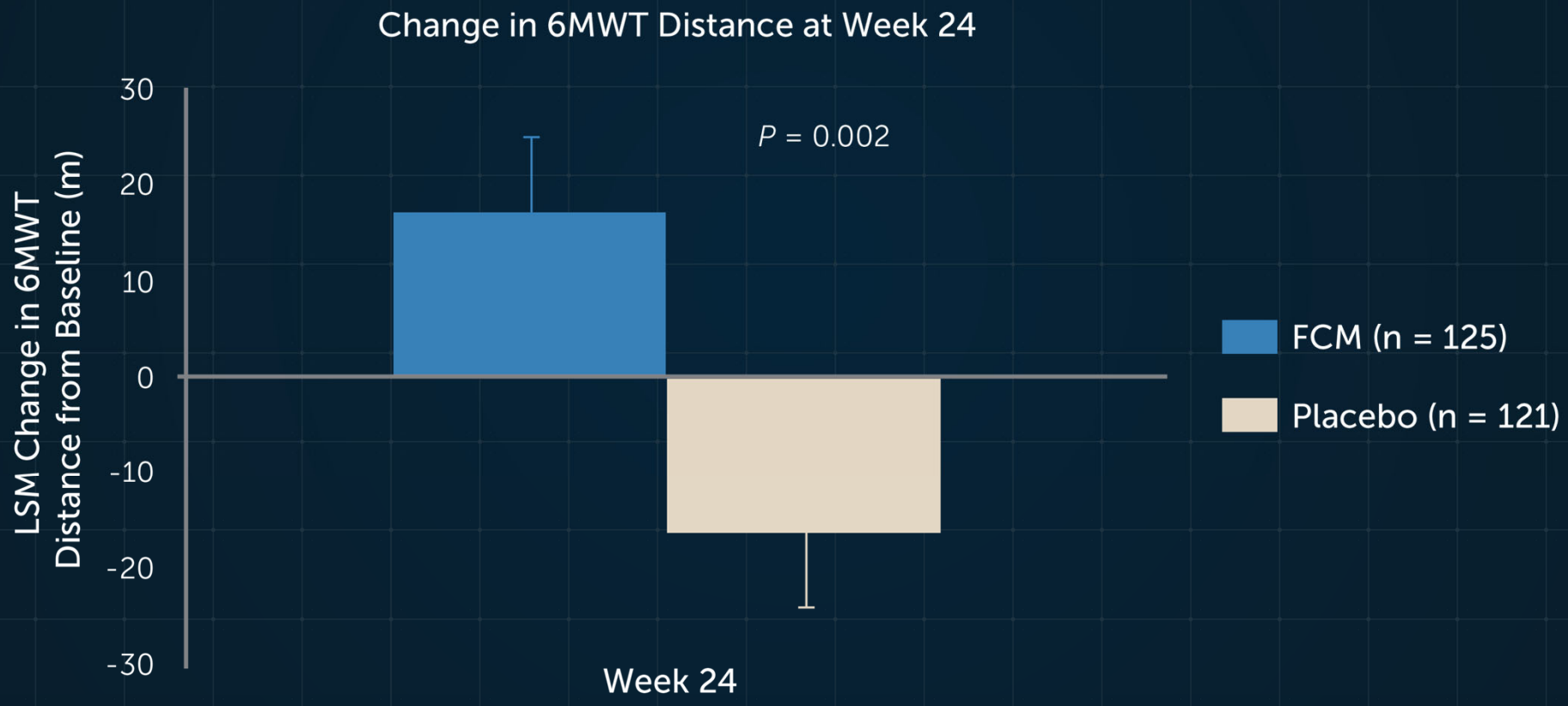
- Females: hemoglobin <12 g/dL (7.5 mmol/L)
- Males: hemoglobin <13 g/dL (8.1 mmol/L)

Patient Case 2

- **Male**
- Class II heart failure
- LVEF 35%
- Hemoglobin 12 g/dL
- Ferritin 185 µg/L
- TSAT 19%

- Diagnosis:
  - Anemic
  - Iron deficient

CONFIRM-HF: IV Iron Improves Exercise Capacity



6MWT, 6-minute walk test; FCM, ferric carboxymaltose; LSM, least squares mean. Ponikowski P, et al. *Eur Heart J*. 2015;36(11):657-668.

Meta-analysis: FCM in HFrEF

Data from FAIR-HF, FER-CARS-01, EFFICACY-HF, and CONFIRM-HF:
HFrEF and iron deficiency, N = 839

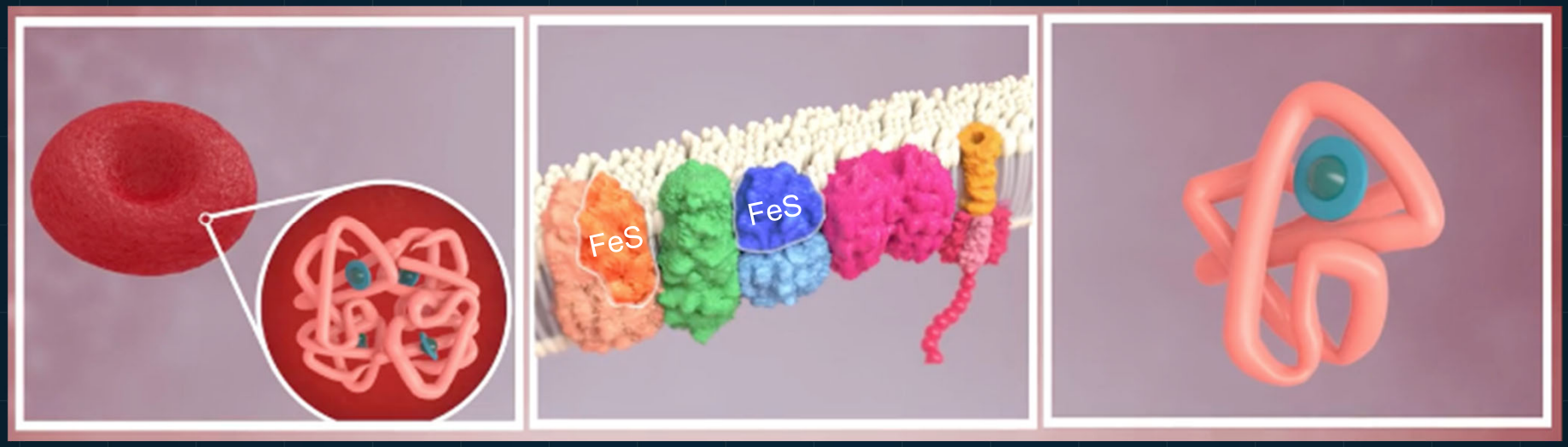
Recurrent Event Outcomes	HR (95% CI)	*P* value
CV hospitalizations and CV mortality	0.59 (0.40-0.88)	0.009
HF hospitalizations and CV mortality	0.53 (0.33-0.86)	0.011
CV hospitalizations and all-cause mortality	0.60 (0.41-0.88)	0.009
HF hospitalizations and all-cause mortality	0.54 (0.34-0.87)	0.011
All-cause hospitalizations and all-cause mortality	0.73 (0.52-1.01)	0.060
HF hospitalizations	0.41 (0.23-0.73)	0.003
CV hospitalizations	0.54 (0.36-0.83)	0.004
All-cause hospitalizations	0.71 (0.50-1.01)	0.056

CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
Anker SD, et al. *Eur J Heart Fail.* 2018;20(1):125-133.

Misconception #4

Only iron deficiency anemia leads to symptoms and poor outcomes.

Essential Roles of Iron



Oxygen transport:
hemoglobin

Energy generation:
electron transport chain

Oxygen storage:
myoglobin

Jankowska EA, et al. *Eur Heart J*. 2013;34(11):816-29.
Wong CC, et al. *Heart Lung Circ*. 2016;25(3):209-16.

Take-home Messages

- Iron deficiency is common in heart failure
- Iron deficiency is observed regardless of anemia status
- Iron deficiency is a separate disease entity
- Screen for iron deficiency regardless of symptoms
- Iron deficiency is a risk factor and treatment matters