Ferric Carboxymaltose Assessment In Patients With IRon Deficiency And Chronic Heart Failure With And Without Anemia (FAIR-HF)

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Disclosures: FAIR-HF was sponsored by Vifor Pharma Ltd., Switzerland. Members of the FAIR-HF executive committee received honoraria from Vifor Pharma Ltd for consultancy and speaking; some received honoraria from Amgen Inc, Roche Pharma and Teva for speaking.

In Memoriam

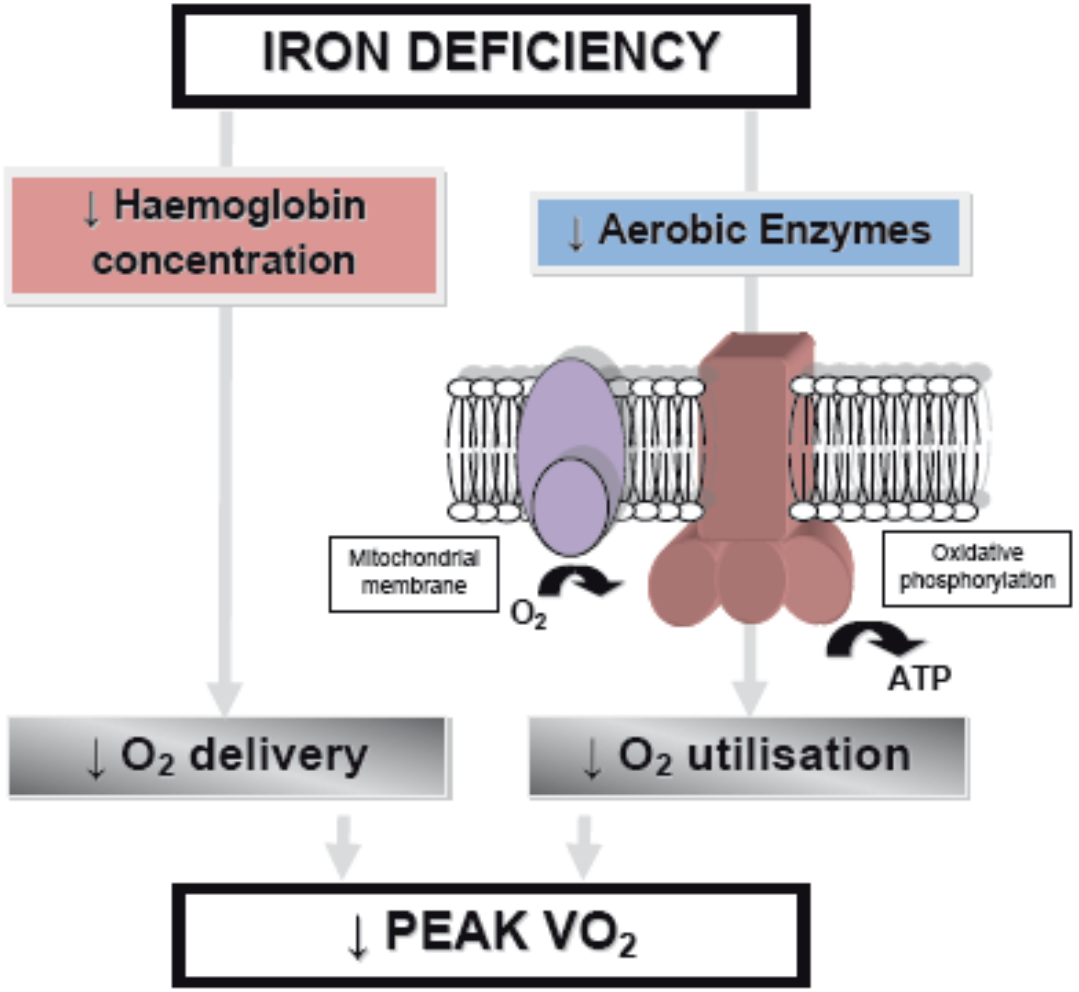
Philip A. Poole-Wilson

Helmut Drexler

Can Iron Repletion Have an Impact in CHF Patients?

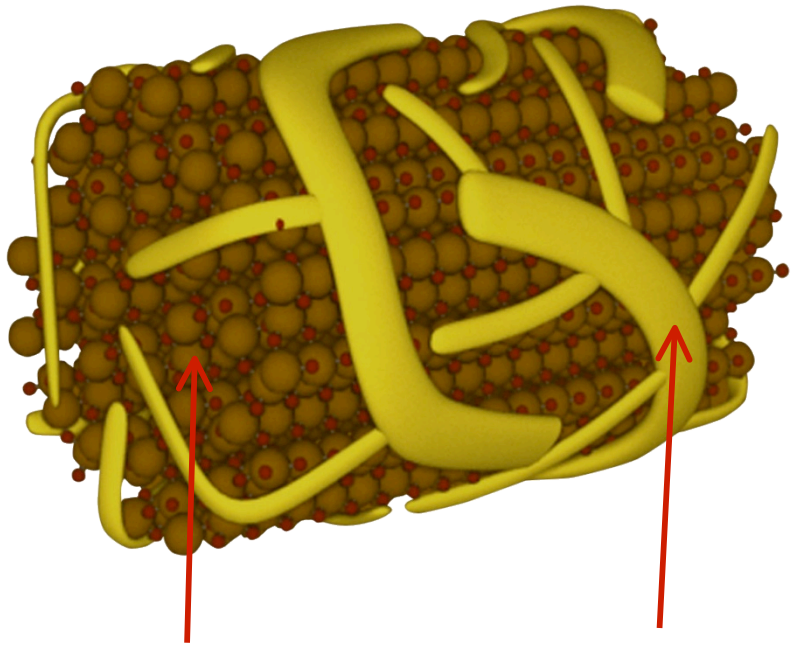
FAIR-HF

- Iron deficiency and anemia are common in HF patients
- Anemia is associated with worsening HF symptoms, increased morbidity & mortality
- Iron deficiency is a major reason for development of anemia
- Iron is essential for oxygen metabolism and energy production



What is Ferric Carboxymaltose?

- Stable polynuclear iron complex
- Essentially no release of ionic iron in the circulation
- Dextran-free carbohydrate shell (low immunogenic potential)
- No test dose
- Physiological pH and osmolality
- Rapid administration of up to 1000 mg iron



Macdougall and Ashenden, *Adv Chron Kid Dis* 2009;16:117-130

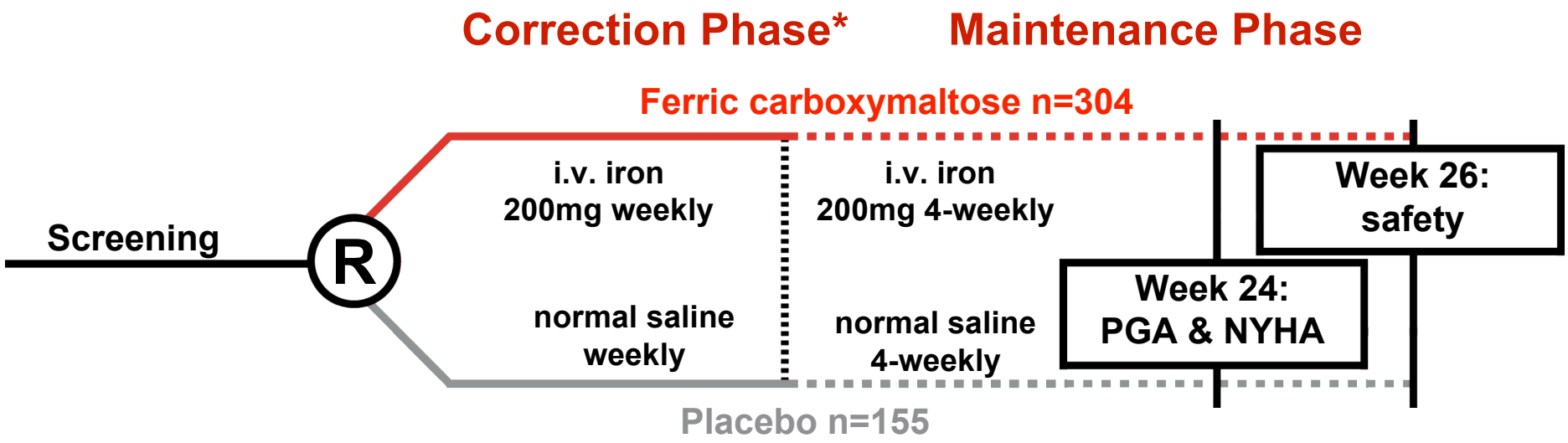
Primary & Secondary Endpoints

- Primary:
  - Self-reported PGA score at week 24
  - NYHA class at week 24 (adjusted for baseline NYHA class)
- Key secondary
  - PGA score and NYHA class* at weeks 4 and 12
  - Six-minute walk test (6MWT) distance**
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) score**
  - European Quality of Life-5 Dimensions (EQ-5D) questionnaire score**
- Safety endpoints

* adjusted for baseline
** at weeks 4, 12 and 24 and adjusted for baseline

Study Design (1/2)

- Statistical considerations:
  - 90% power to detect a difference in PGA score means of 0.900
  - 90% power to detect a difference in NYHA class means of 0.500
  - All tested at 2-sided significance of 0.025
  - Aimed to enroll: 442 patients



*total dose required for repletion
calculated using the Ganzoni formula

Anker *et al, Eur J Heart Failure* 2009;11:1084-1091

Study Design (2/2)

FAIR-HF

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb 95–135g/L
  - Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%
- **Main exclusion criteria:**
  - Uncontrolled hypertension, inflammation (CrP >20 mg/L)
  - Significant liver or renal dysfunction
- **Treatment adjustment algorithm:**
  - Interruption: Hb >160 g/L or ferritin >800 µg/L or ferritin >500 µg/L, if TSAT >50%
  - Restart: Hb <160 g/L and serum ferritin <400 µg/L and TSAT <45%
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections

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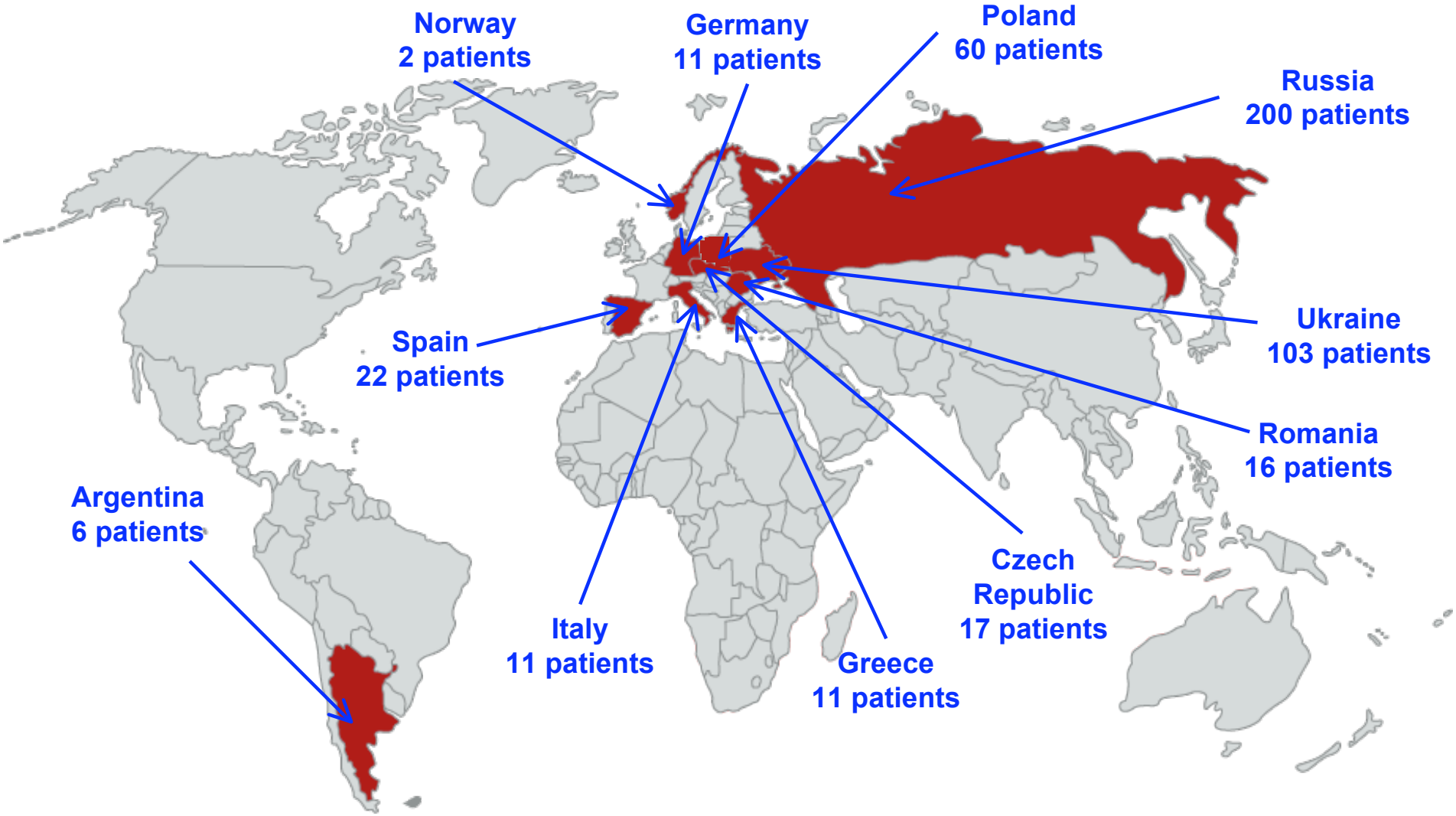
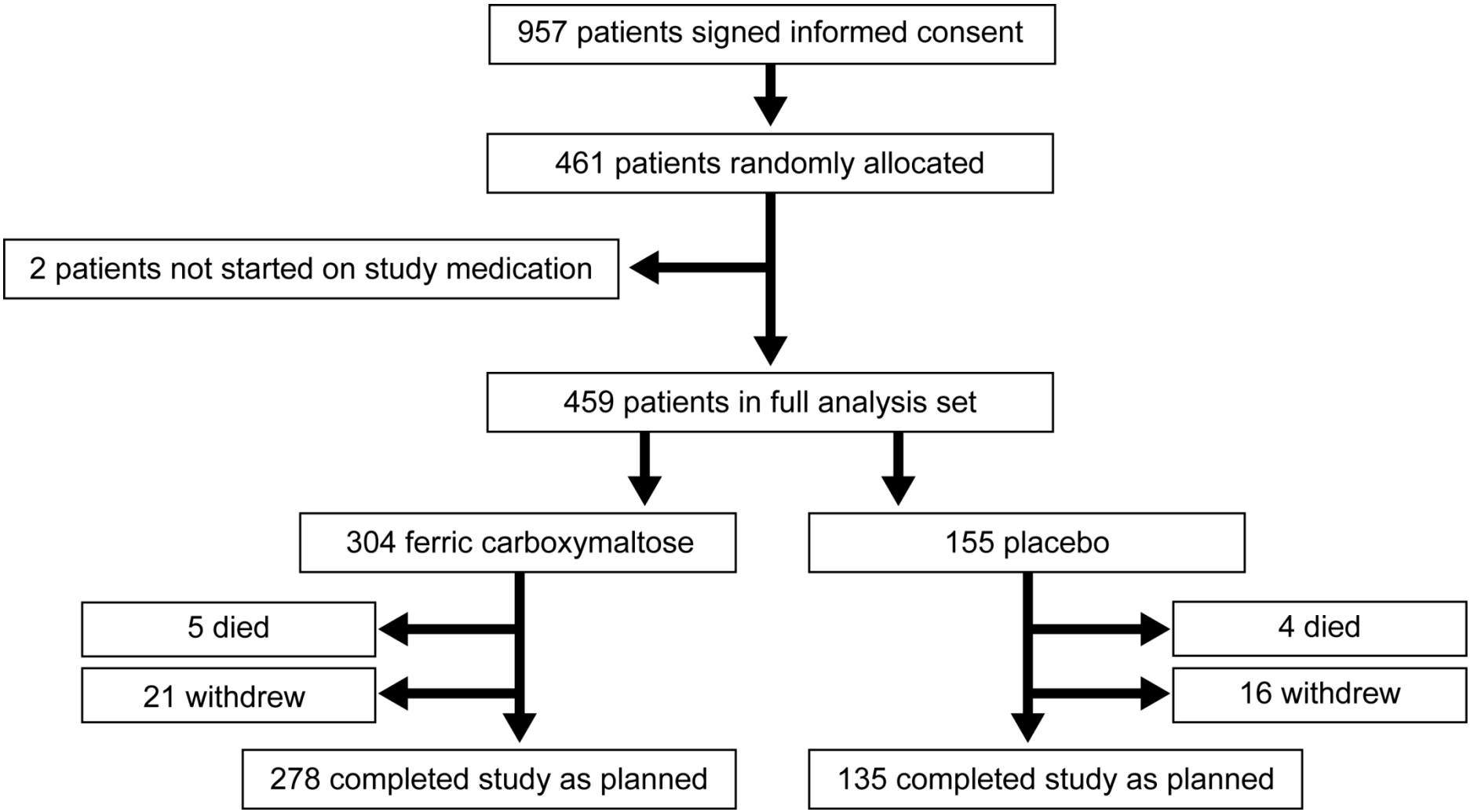
Participating Countries



FAIR-HF Patient Disposition



Demographics (1/2)

FAIR-HF

	FCM (N=304)	Placebo (N=155)
Age (years)	68	67
Gender (% female)	52	55
Ischemic etiology (%)	81	79
Diabetes (%)	31	24
LVEF (%)	32	33
SBP (mm Hg)	126	126
DBP (mm Hg)	77	76
ACEi/ARB (%)	92	91
Beta-Blocker (%)	86	83
Diuretics (%)	92	90

Demographics (2/2)

FAIR-HF

	FCM (N=304)	Placebo (N=155)
NYHA class II, n (%)	53 (17.4)	29 (18.7)
NYHA class III, n (%)	251 (82.6)	126 (81.3)
6-min walk test distance (m)*	274 ± 105	269 ± 109
Hb (g/L)*	119 ± 13	119 ± 14
MCV (μm^3)*	92 ± 8.1	92 ± 6.7
Serum ferritin (µg/L)*	53 ± 55	60 ± 67
TSAT (%)*	17.7 ±12.6	16.7 ± 8.4
CRP (mg/L)*	7.5 ± 5.3	9.1 ± 5.5
Creatinine (mg/dL)*	1.2 ± 0.6	1.2 ± 0.6
Estimated GFR (mL/min/1.73m^2)*	64 ± 21	65 ± 25

*mean ± SD

Just Online

FAIR-HF

The NEW ENGLAND JOURNAL of MEDICINE

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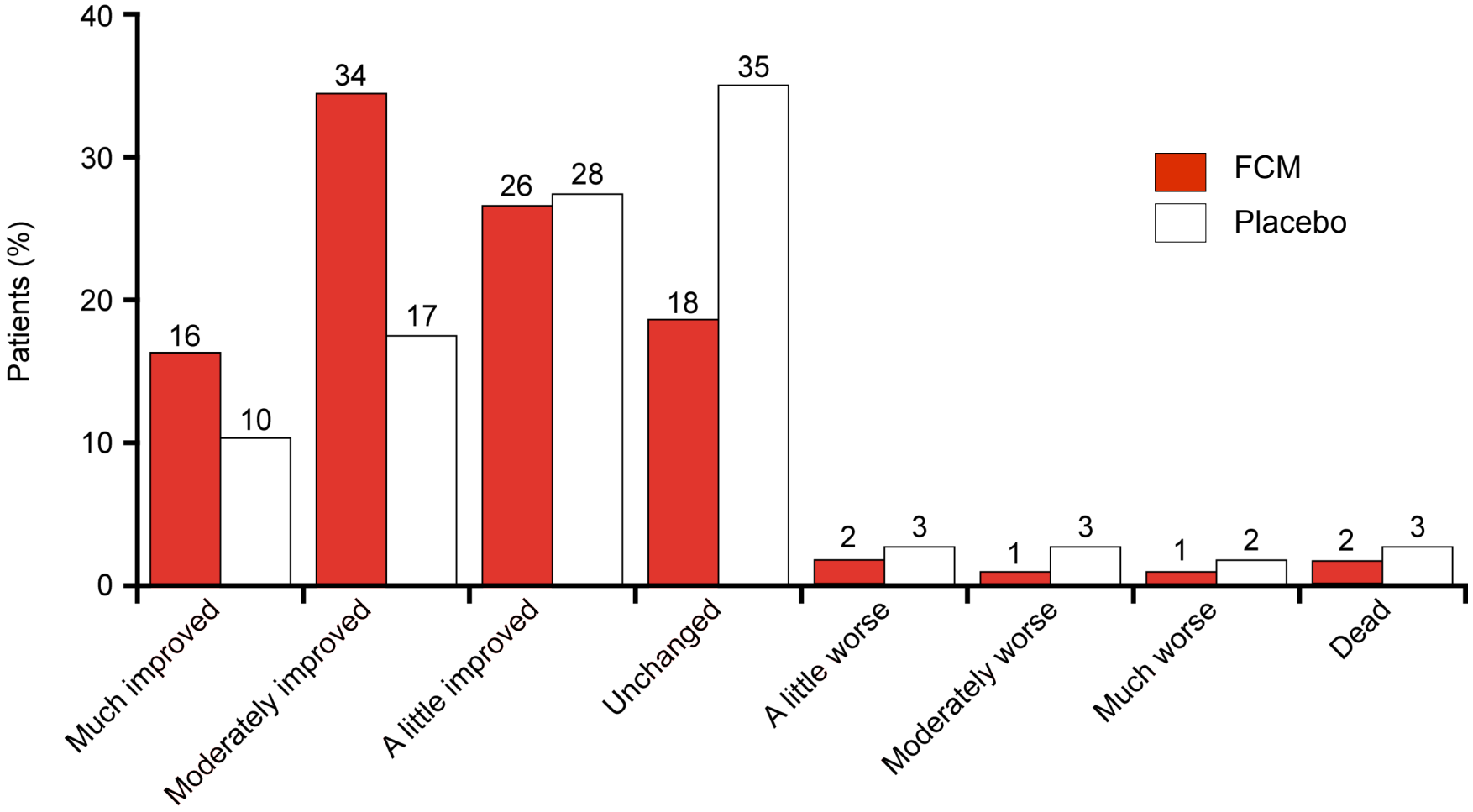
Published online November 17, 2009

Primary Endpoint:
Patient Global Assessment at Week 24

FAIR-HF

FCM improved self-reported PGA scores at week 24

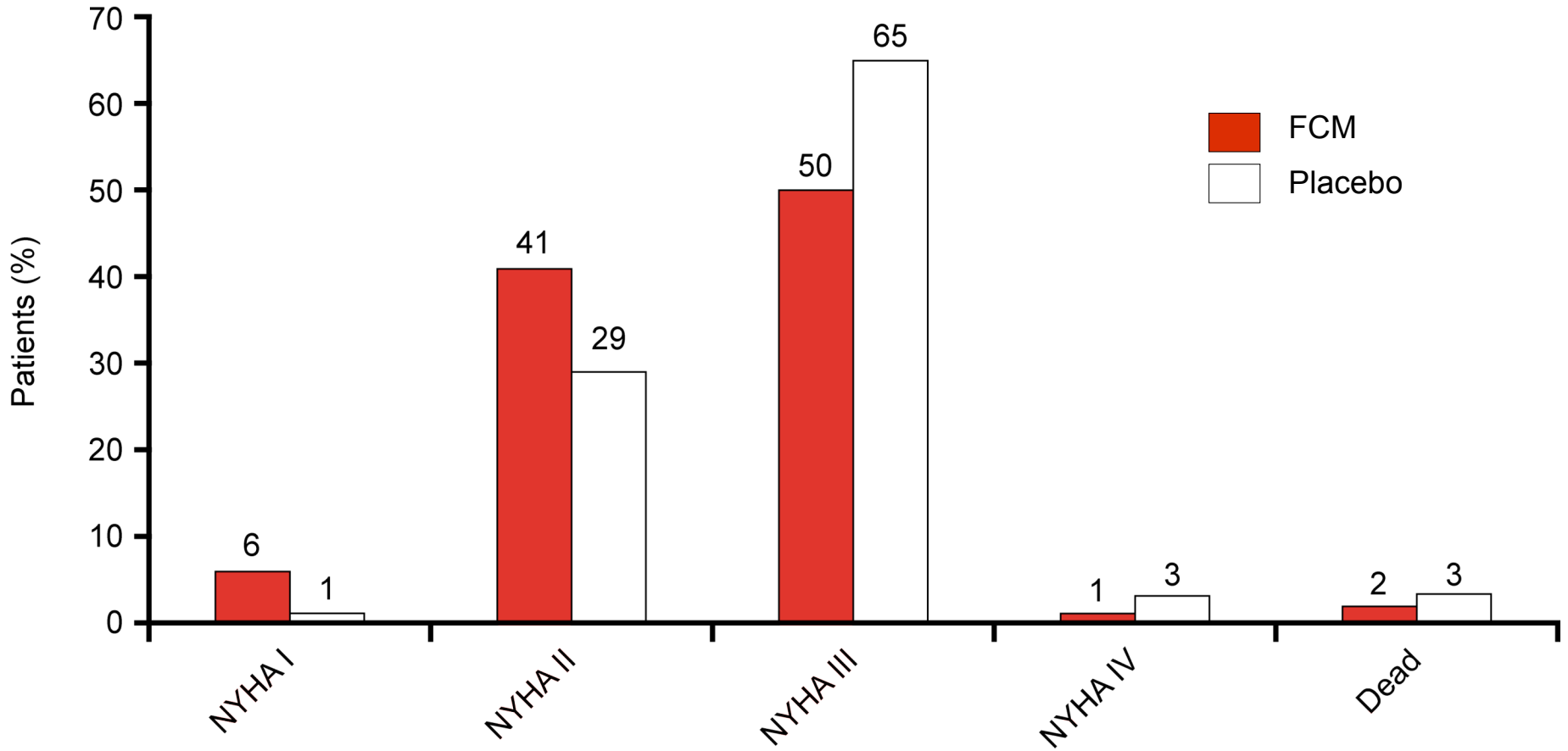
Odds ratio for better rank: 2.51 (95% CI 1.75,3.61), P<0.0001



Primary Endpoint:
NYHA Functional Class at Week 24

FCM improved NYHA functional class at week 24

Odds ratio for improvement by 1 class: 2.40 (95% CI 1.55,3.71), P<0.0001*

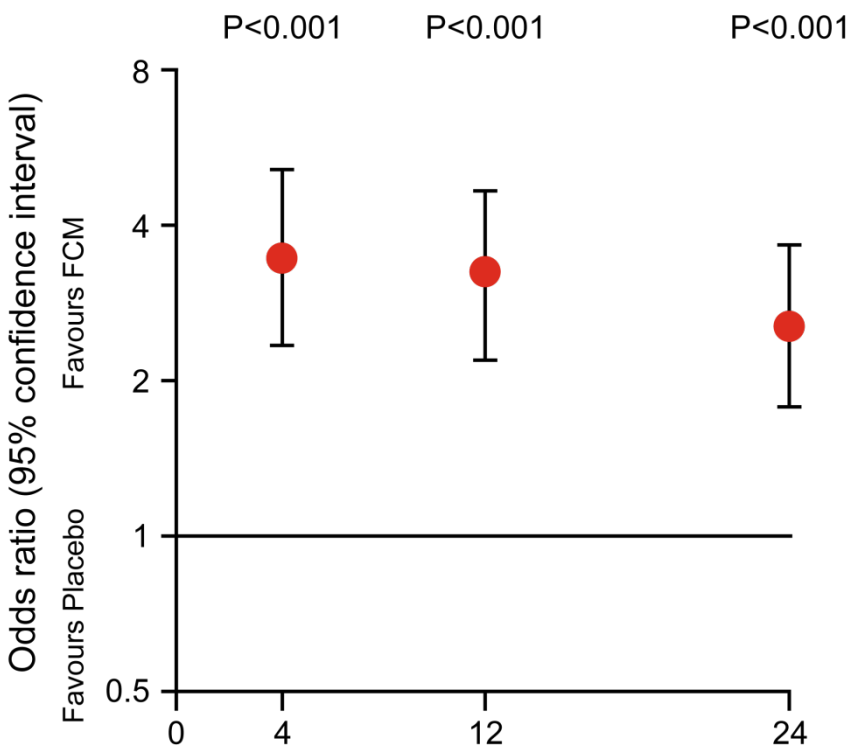


*adjusted for baseline

Secondary Endpoint: PGA & NYHA Functional Class Over Time

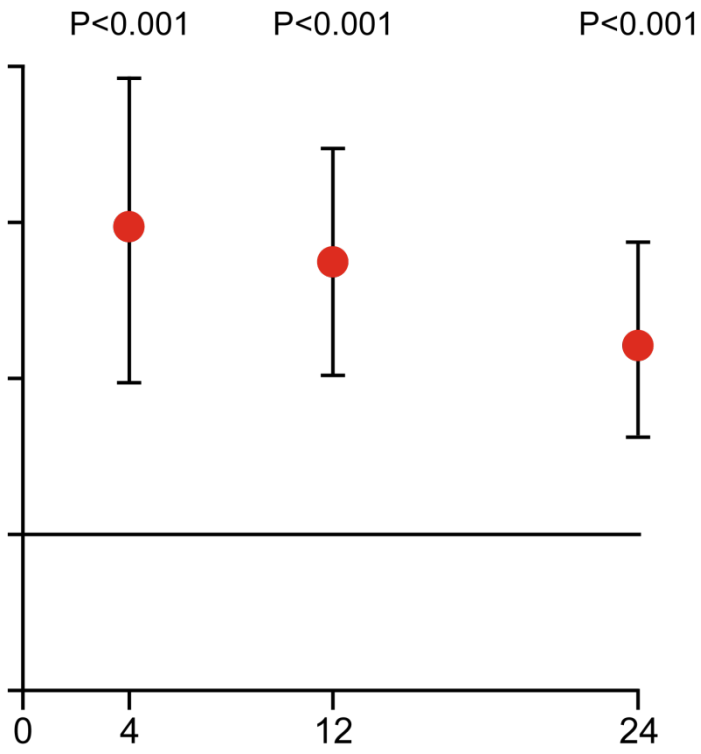
FAIR-HF

Self-reported Patient Global Assessment Score



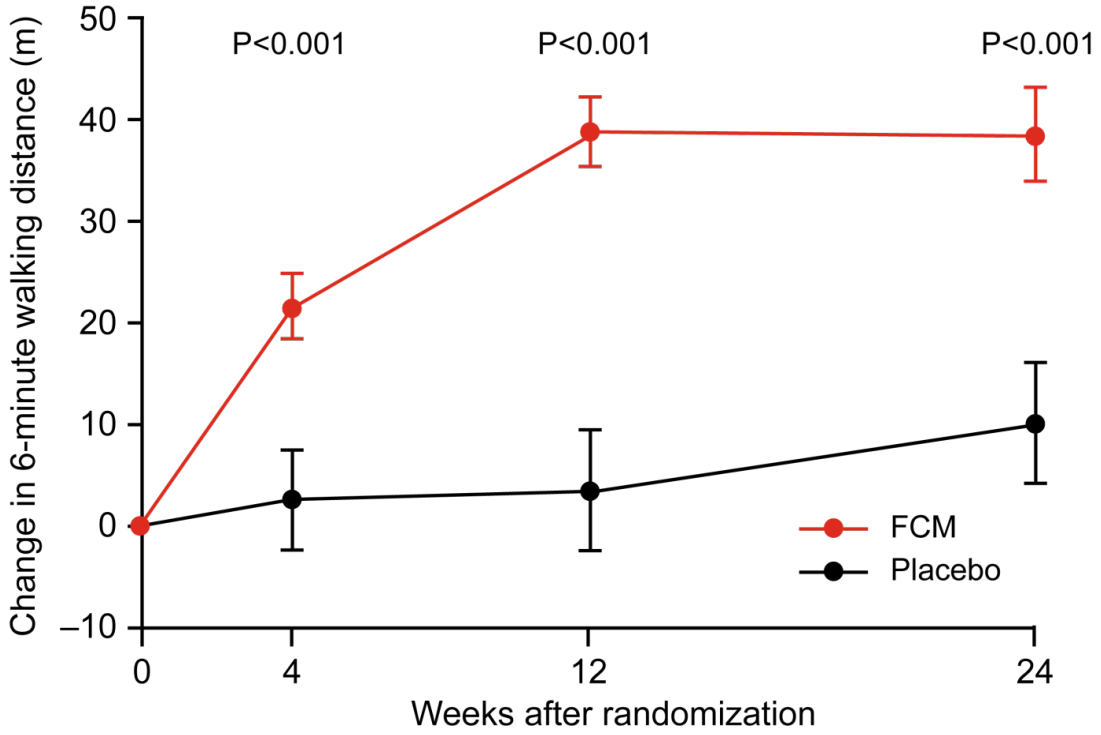
no. of patients			
FCM	282	291	292
Placebo	146	149	149

New York Heart Association Functional Score



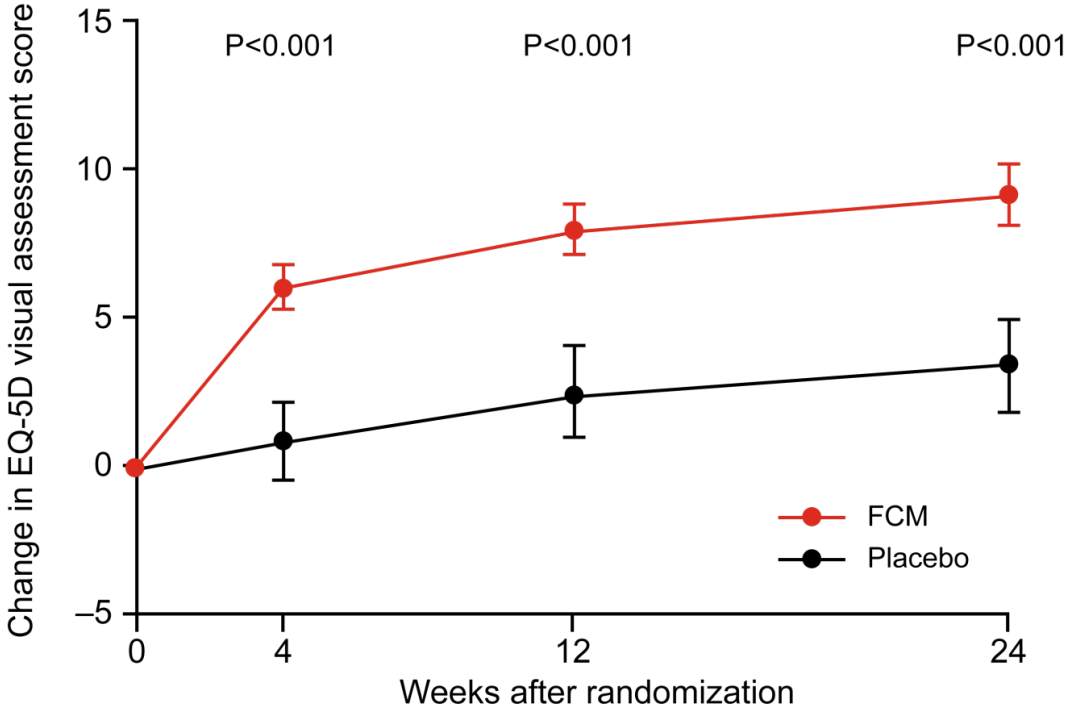
304	287	294	294
155	147	150	150

Secondary Endpoint: Six-Minute Walk Test at Week 4, 12 & 24



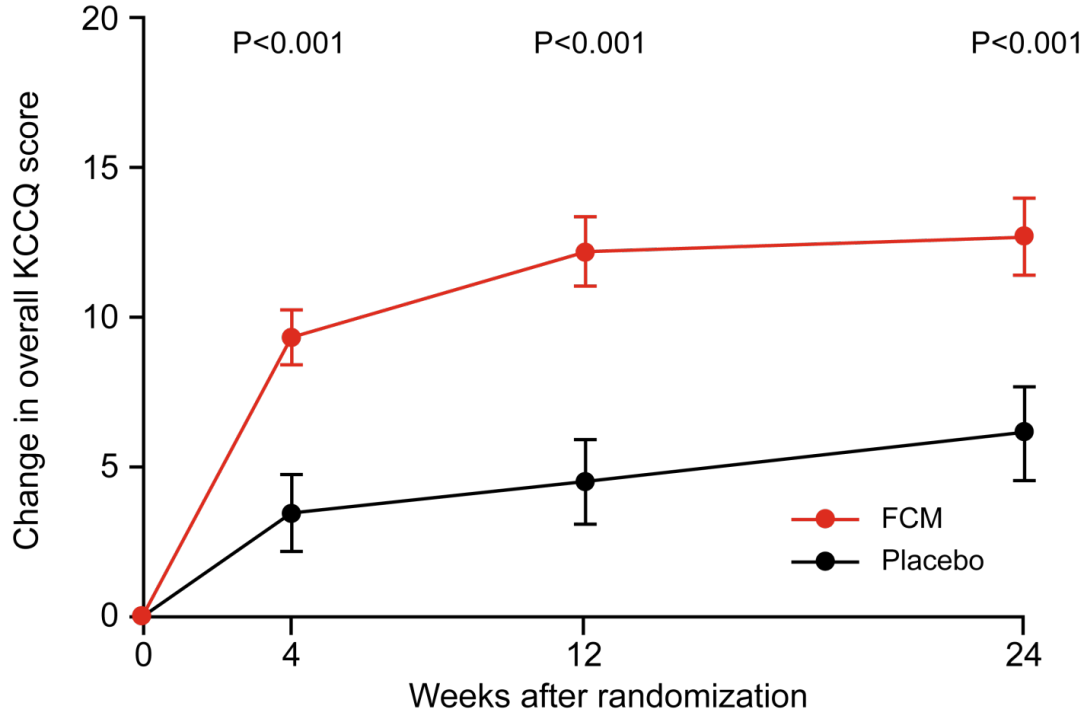
FCM				
No. of patients	303	284	280	268
Distance (mean±SE)	274±6	294±7	312±6	313±7
Placebo				
No. of patients	155	144	141	134
Distance (mean±SE)	269±9	269±10	272±10	277±10
Treatment effect (mean±SE)		21±6	37±7	35±8

Secondary Endpoint: EQ-5D (QoL) Score at Week 4, 12 & 24



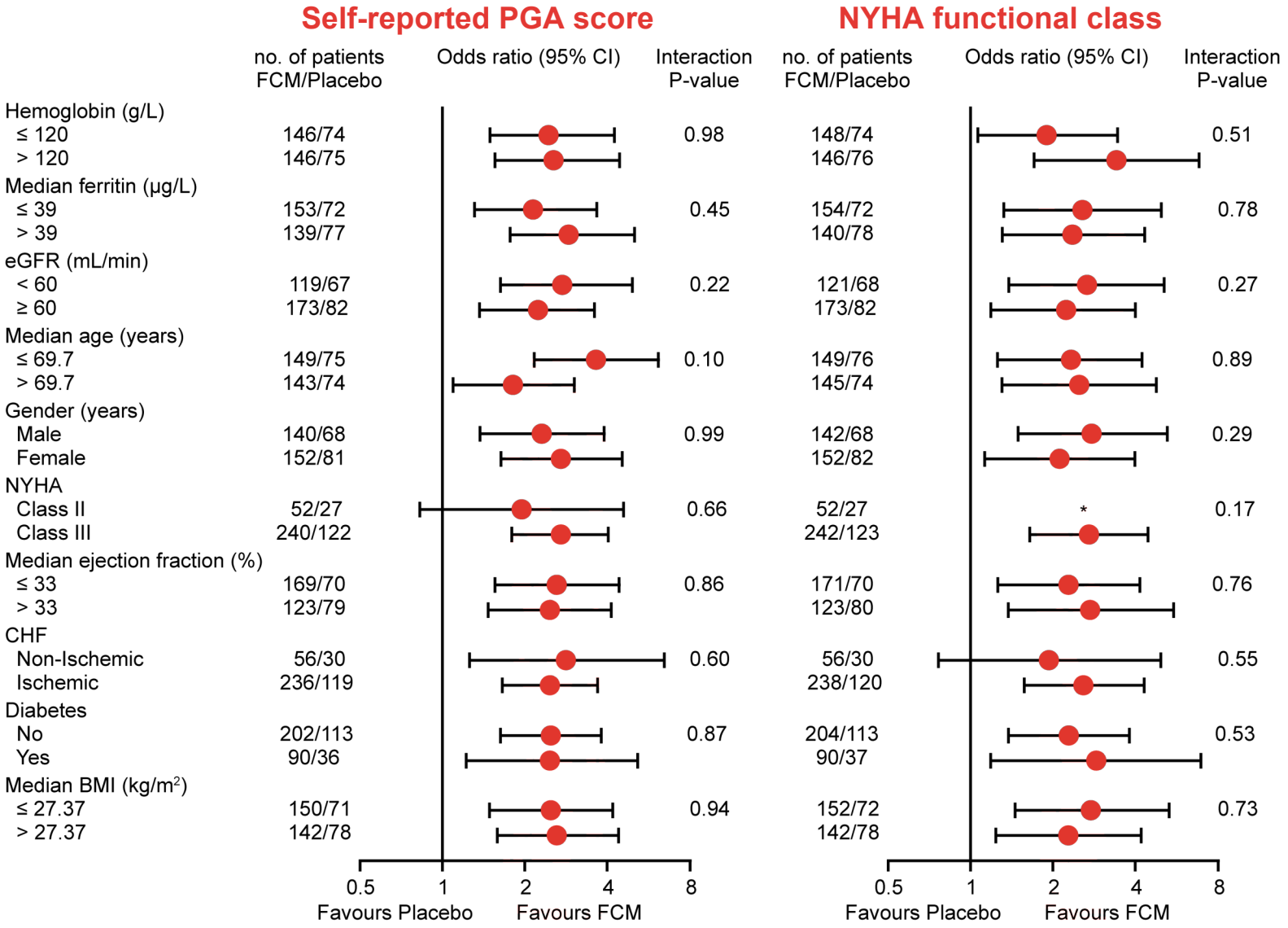
FCM				
No. of patients	295	274	283	285
Score (mean±SE)	54±1	60±1	62±1	63±1
Placebo				
No. of patients	152	140	145	146
Score (mean±SE)	54±1	54±2	56±2	57±2
Treatment effect (mean±SE)		6±1	6±2	7±2

Secondary Endpoint: KCCQ (QoL) Score at Week 4, 12 & 24



FCM				
No. of patients	297	277	286	286
Score (mean±SE)	52±1	62±1	65±1	66±1
Placebo				
No. of patients	151	140	144	145
Score (mean±SE)	53±1	56±2	57±2	59±2
Treatment effect (mean±SE)		6±1	8±2	7±2

Secondary Endpoints: PGA & NYHA in Predefined Subgroups



Safety Endpoints

FAIR-HF

	Patients with events (Incidence per 100-patient years at risk)		
	FCM (N=305)	Placebo (N=154)	P
Death	5 (3.4)	4 (5.5)	0.47
CV death	4 (2.7)	4 (5.5)	0.31
Death due to worsening HF	0 (0.0)	3 (4.1)	-
First hospitalization	25 (17.7)	17 (24.8)	0.30
Hospitalization for any CV reason	15 (10.4)	14 (20.0)	0.08
First hospitalization for worsening HF	6 (4.1)	7 (9.7)	0.11
Any hospitalization or death	30 (21.2)	19 (27.7)	0.38
Hospitalization for any CV reason or death	20 (13.9)	16 (22.9)	0.14
First hospitalization for worsening HF or death	11 (7.5)	10 (13.9)	0.15

Reported Adverse Events

	Patients with events (Incidence per 100-patient years at risk)		
	FCM (N=305)	Placebo (N=154)	P
Cardiac disorder	38 (27.6)	33 (50.2)	0.01
Gastrointestinal disorder	24 (16.9)	5 (6.9)	0.06
General disorder or administration site condition	23 (16.2)	6 (8.3)	0.14
Injection site pain or discoloration	6 (4.1)	0 (0.0)	-
Infection or infestation	50 (37.0)	24 (35.8)	0.97
Abnormal laboratory test, vital sign, physical finding	32 (23.0)	10 (14.0)	0.17
Nervous system disorder	22 (15.6)	14 (20.3)	0.44
Respiratory, thoracic or mediastinal disorder	9 (6.2)	10 (14.2)	0.06
Vascular disorder	20 (14.0)	11 (15.7)	0.80

No severe or serious hypersensitive reactions

Adverse events are classified by the Medical Dictionary for Regulatory Activities (MedDRA) and are reported by system organ class when they occurred for more than 4% of patients in total.

Conclusions

In symptomatic patients with chronic heart failure and iron deficiency, 24 weeks of treatment with i.v. ferric carboxymaltose significantly improved:

- self-reported health status
- NYHA functional class, i.e. shortness of breath
- functional capacity
- quality of life measures

These results were seen in iron deficient HF patients with & without anemia.

Ferric carboxymaltose was well tolerated.

Implications for Clinical Practice

Iron deficiency:

- is an important therapeutic target in patients with HF
- can easily be detected using a simple blood test
- should be assessed in all symptomatic patients with HF

If iron deficiency is diagnosed, i.v. iron (e.g. ferric carboxymaltose) should be considered to improve the patient‘s symptoms.

Thank You

Patients

Investigators

Executive Committee

DSMB

Vifor Pharma