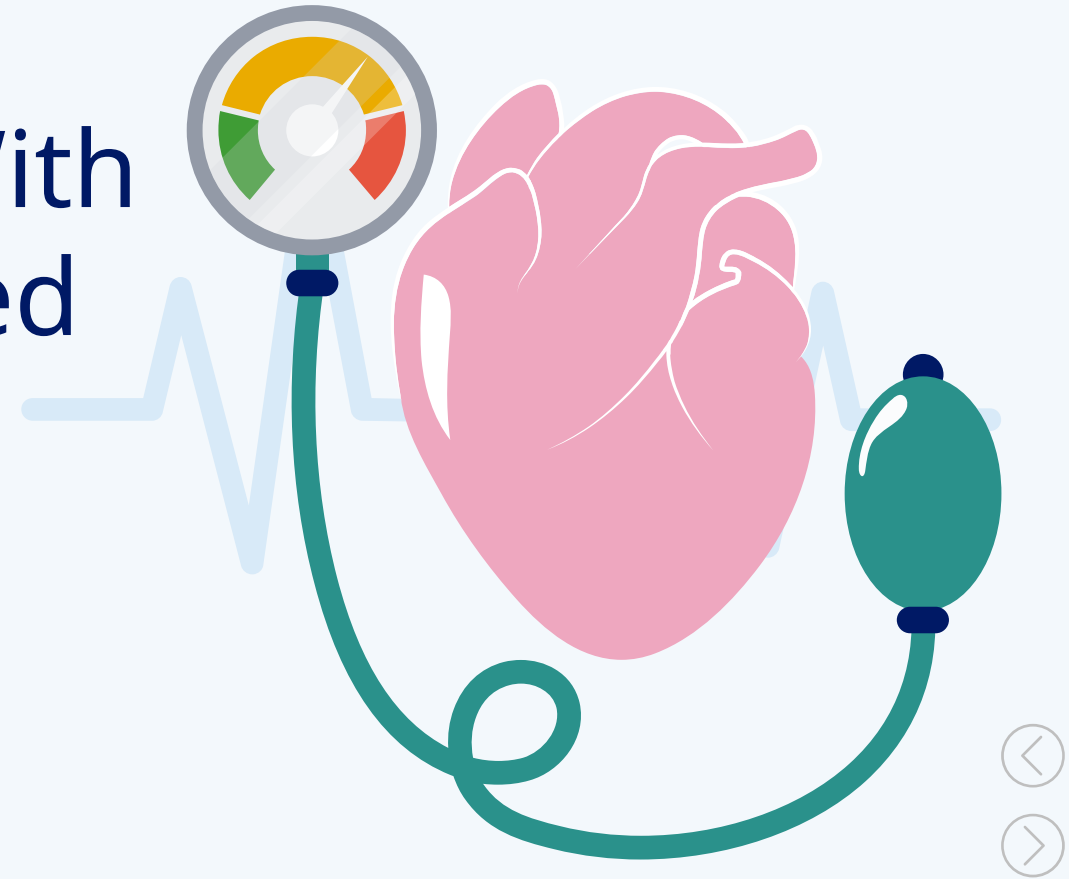


Interleukin-6 in Patients With Heart Failure and Preserved Ejection Fraction



Study objectives and methods

Post-hoc analysis (N = 374) of 4 NIH sponsored studies (RELAX, NEAT, INDIE, INABLE)



Objective:

To determine how IL-6 relates to changes in cardiac function, congestion, body composition, and exercise tolerance in HFpEF



Inclusion criteria:

Signs and symptoms of HFpEF
Objective evidence of HFpEF characterized by a previous HF hospitalization



Assessments:*

- ✓ Biomarker
- ✓ Echocardiography (resting and peak)
- ✓ Cardiopulmonary exercise testing
- ✓ 6MWT
- ✓ Body composition[†]
- ✓ Resting metabolic rate[†]
- ✓ Submaximal treadmill testing[†]

*According to available number of patients; [†]Only participants in INABLE; 6MWT, 6-minute walk test
6MWT, 6-minute walk test; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IL-6, Interleukin 6; NIH, National Institutes of Health
Alogna A et al. JACC Heart Fail. 2023;S2213-1779(23)00384-0



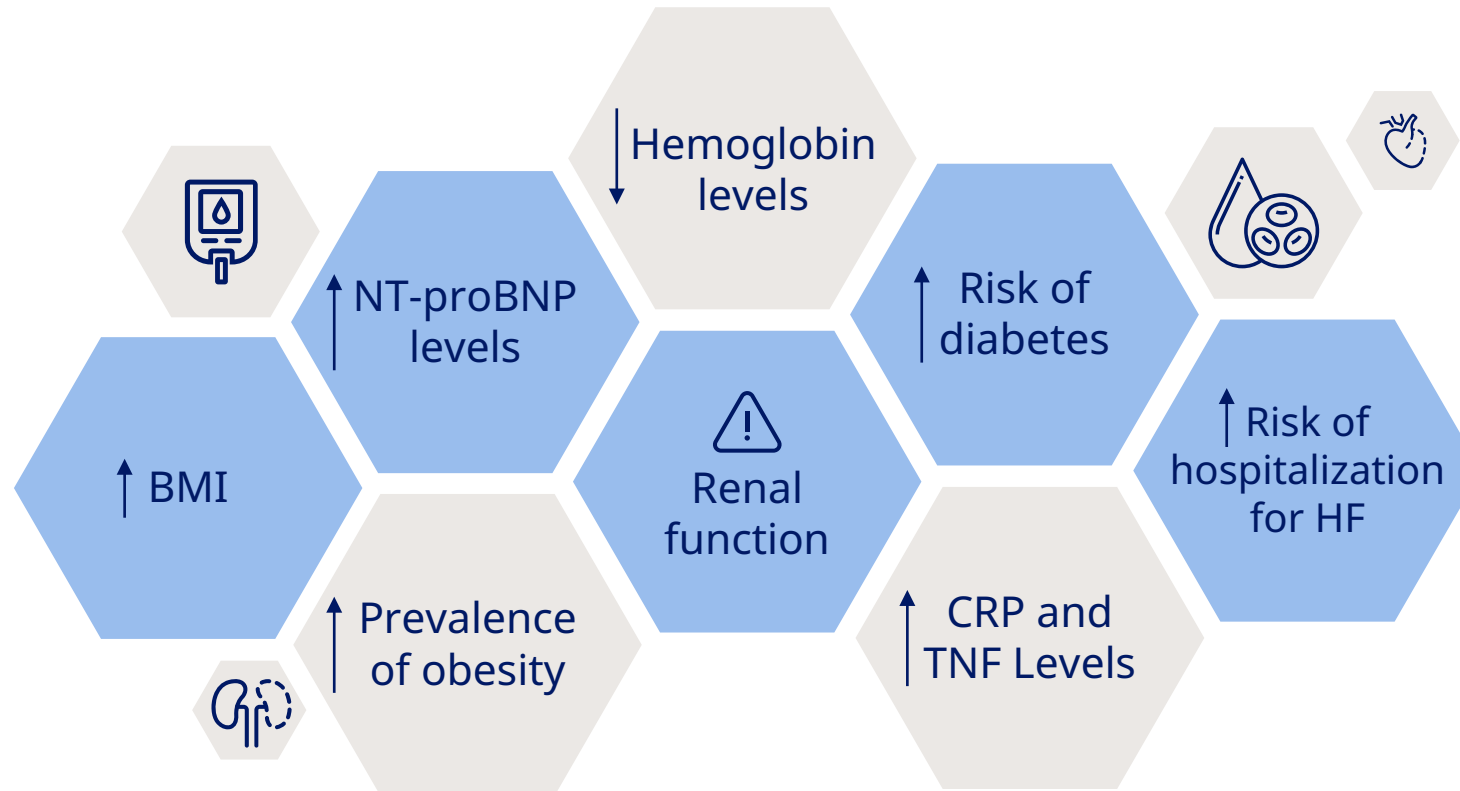
Baseline Characteristics Across All 4 Studies

	Total Cohort (N = 374)	IL-6 Tertile 1 (<1.16 pg/mL; n=124)	IL-6 Tertile 2 (1.16-2.01 pg/mL; n=124)	IL-6 Tertile 3 (>2.01 pg/mL; n=126)	P Value
Age, Y	69 ± 10	69 ± 10	68 ± 10	69 ± 10	0.72
Women	173 (46)	51 (41)	64 (52)	58 (46)	0.253
BMI, kg/m²	35 ± 7	32 ± 6	35 ± 7	37 ± 7	<0.0001
Comorbidities					
Obesity	269 (72)	70 (57)	95 (77)	104 (83)	<0.0001
Diabetes	139 (37)	38 (31)	40 (32)	61 (48)	0.006
Hypertension	315 (84)	102 (82)	106 (86)	107 (85)	0.758
Atrial fibrillation	181 (49)	54 (44)	64 (52)	63 (50)	0.441
HF hosp. 1 y, n = 322	83 (26)	22 (20)	26 (23)	35 (35)	0.055
Medications					
Beta blockers	261 (70)	79 (64)	86 (69)	96 (76)	0.099
ACEI or ARB	218 (58)	76 (61)	81 (65)	61 (48)	0.018
Diuretics	311 (83)	93 (75)	103 (83)	115 (91)	0.003
Laboratory indices					
NT-proBNP, pg/mL	425 (132,960)	353 (91,861)	419 (119,949)	498 (178,1262)	0.026
NT-proBNP _{SR} , pg/mL	172 (76,475)	158 (54,486)	128 (66,464)	282 (109,546)	0.035
NT-proBNP _{AF} , pg/mL	796 (362,1414)	746 (337,1355)	796 (377,1448)	885 (450,1593)	0.479
Creatinine, mg/dL	1.19 ± 0.40	1.11 ± 0.29	1.18 ± 0.45	1.27 ± 0.44	0.007
eGFR, mL/min/1.73 m ²	60 (47,76)	60 (51,79)	64 (47,76)	57 (44,76)	0.044
Hemoglobin, g/dL	13.0 ± 1.5	13.4 ± 1.4	12.9 ± 1.4	12.7 ± 1.6	0.001
IL-6 (pg/mL)	1.58 (0.97,2.37)	0.83 (0.62,0.97)	1.57 (1.37,1.80)	2.74 (2.31,3.84)	NA
hsCRP (mg/L)	3.52 (1.51,7.43)	1.70 (0.96,3.60)	3.57 (1.79,7.45)	6.74 (3.32, 11.83)	<0.0001
TNF-α (pg/mL)	4.46 (3.48,6.05)	3.99 (3.16,5.18)	4.23 (3.47,5.37)	5.49 (4.05,7.10)	<0.0001
Functional capacity					
6MWD, m	329 (248,396)	359 (265,431)	335 (253,400)	291 (184,335)	<0.0001
VO ₂ , mL/min/kg	13.3 ± 3.5	14.4 ± 3.9	13.1 ± 3.1a	12.3 ± 3.3	<0.0001

6MWD, 6 minute walk distance n,223; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF hosp. 1 y, heart failure hospitalization in the previous year n, 322; IL, interleukin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NT-proBNP_{SR}, NT-proBNP in sinus rhythm; NT-proBNP_{AF}, NT-proBNP in atrial fibrillation; TNF, tumor necrosis factor; VO₂, peak oxygen consumption
 Alogna A et al. JACC Heart Fail. 2023;S2213-1779(23)00384-0

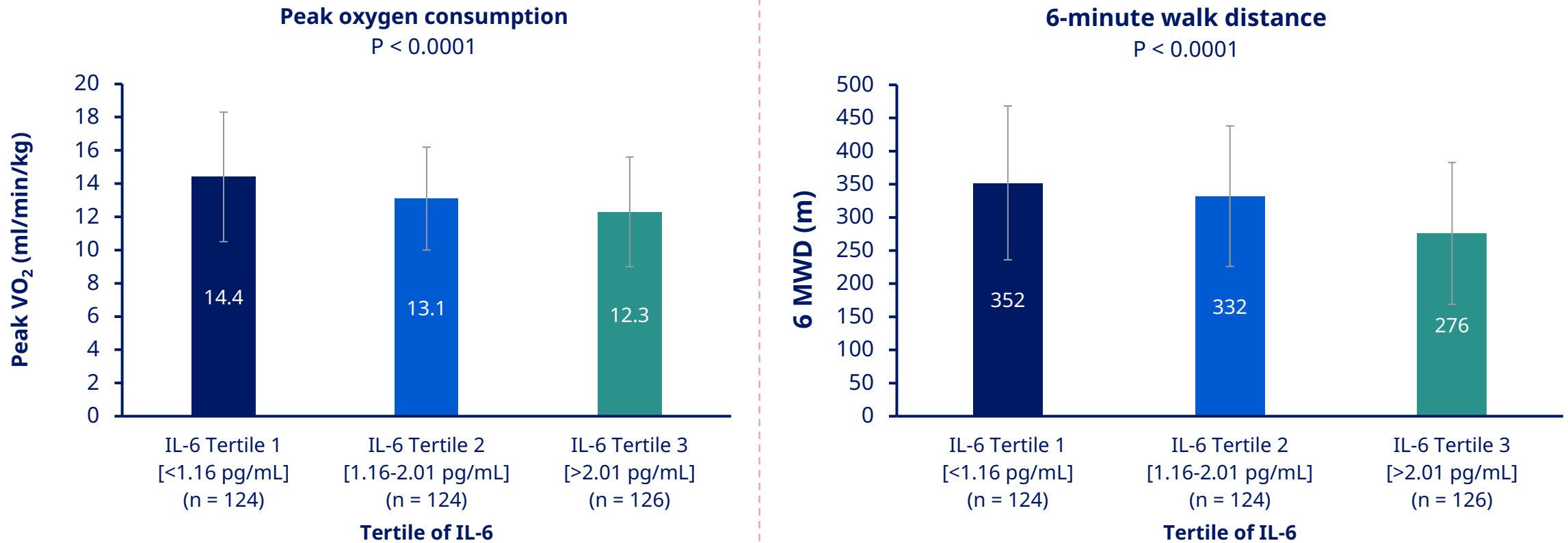
Patient characteristics by IL-6 level

Patients with HFpEF and highest IL-6 levels had a



There were no differences in cardiac structure and function at rest as a function of IL-6 levels

Comparison of exercise capacity by IL-6 level



Patients with HFpEF and highest IL-6 concentrations had more severe impairments in exercise capacity, reflected both by lower 6MWD and decreased peak VO₂, even after accounting for increases in IL-6 related to excess body mass

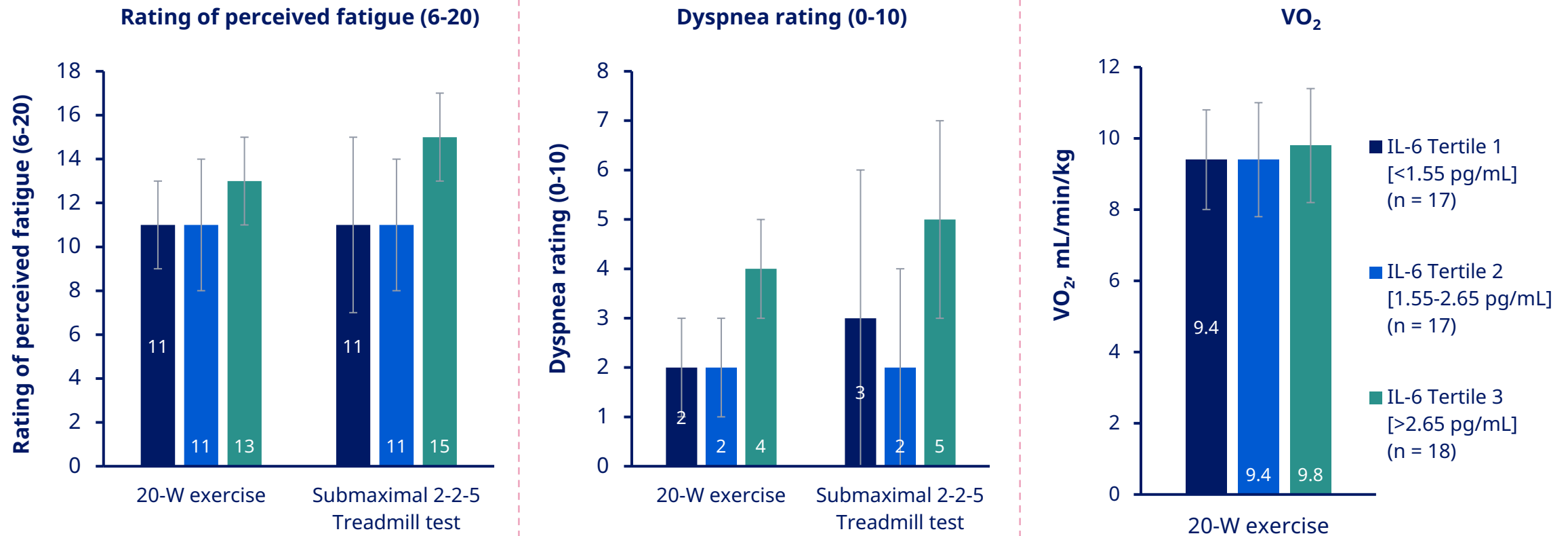
Comparison of exercise capacity by IL-6 level adjusted for BMI

IL-6 levels were modestly and directly correlated with BMI

As compared with patients with IL-6 relative to BMI in the lowest tertile, those in the highest tertile had



Submaximal exercise and symptom assessment in INABLE



Patients with HFpEF and higher IL-6 levels again reported more severe symptoms of fatigue and dyspnea

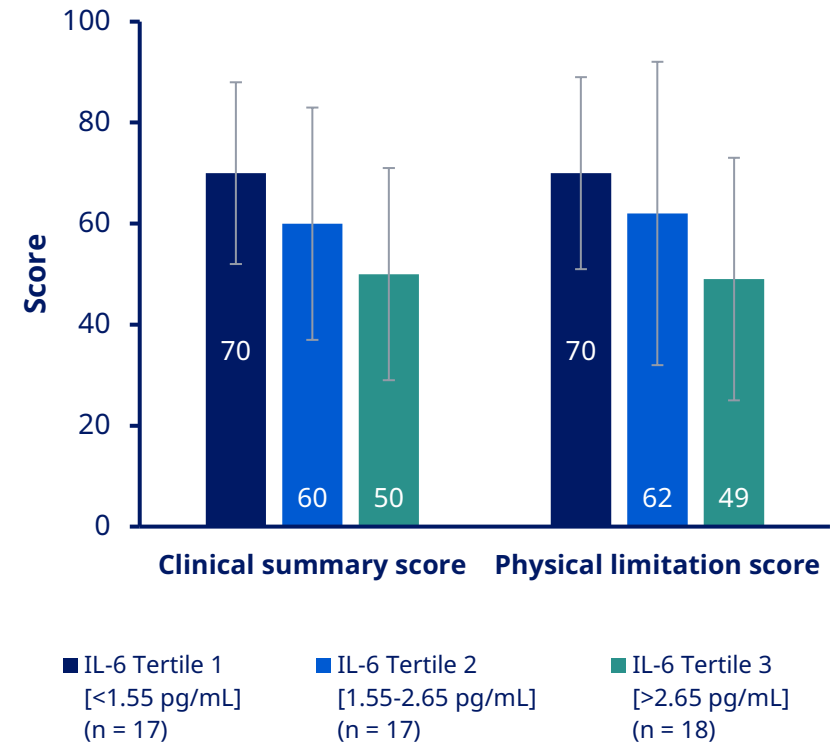
6-20 and 0-10 are ratings of perceived exertion. 20-W and 2-2-5 are exercise tests. Please see slide notes for definitions
 HFpEF, heart failure with preserved ejection fraction; IL, interleukin; VO₂, peak oxygen consumption
 Alogna A et al. JACC Heart Fail. 2023;S2213-1779(23)00384-0

Body Composition and Health Status in INABLE

Body composition by tertile of IL-6

	IL-6 Tertile 1 [<1.55 pg/mL] (n = 17)	IL-6 Tertile 2 [1.55-2.65 pg/mL] (n = 17)	IL-6 Tertile 3 [>2.65 pg/mL] (n = 18)	P value
Total body weight, kg	90 ± 15	106 ± 21	108 ± 30	0.057
Ideal body weight, kg	64 ± 9	64 ± 7	63 ± 9	0.844
Excess body weight, kg	26 ± 10	42 ± 18	45 ± 28	0.010
Fat weight, kg	36 ± 8	47 ± 14	51 ± 24	0.038
Fat, %	42 ± 6	47 ± 8	47 ± 9	0.085
Lean weight, kg	50 ± 8	53 ± 11	53 ± 10	0.682
Lean, %	57 ± 7	52 ± 8	51 ± 9	0.073

Patient-Reported Health Status (KCCQ)



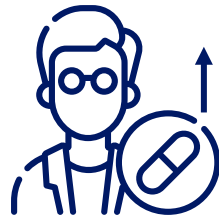
Higher IL-6 levels are associated with increases in body fat, changes in body composition and poor patient-reported health status

Summary

High IL-6 levels associated with



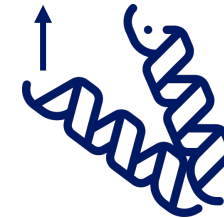
↑ BMI



↑ Comorbidity



↑ NT-proBNP



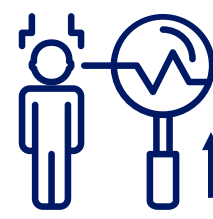
↑ CRP



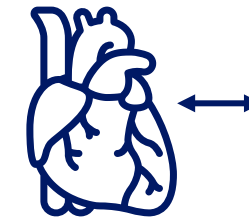
↑ TNF-α



↑ Total body
and trunk fat



↑ Symptoms



↔ Cardiac structure
and function

↓ Maximal and submaximal exercise capacity

