

In F0-F1 and F2-F3 MASH, ≥ 5% weight loss significantly lowers VCTE and ELF™ independent of biopsy fibrosis improvement; resmetirom and not placebo reduction of ELF and VCTE are associated with biopsy improvement of fibrosis, independent of weight loss

POSTER
LBP-024

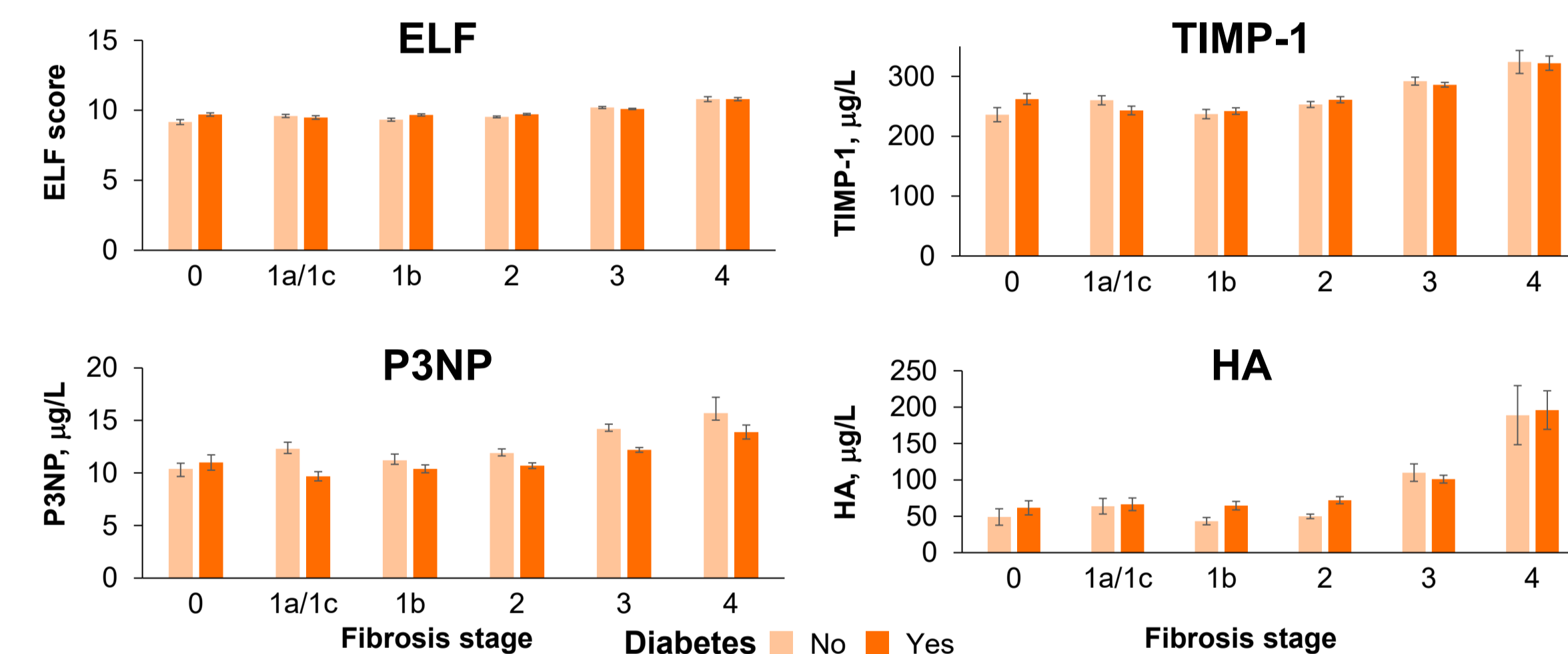
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INTRODUCTION

- Resmetirom is a once-daily, oral, liver-directed THR-β-selective agonist approved for the treatment of adults with MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3), in conjunction with diet and exercise, in the United States and EU¹⁻²
- Changes in liver stiffness (e.g. VCTE) and ELF, a prognostic test for advanced (F3-F4) fibrosis, are proposed as surrogate end points for histologic fibrosis response in MASH³⁻⁵
- ELF and its components (HA, P3NP, and TIMP-1) are similar in people with MASLD and F0-F2 fibrosis and increase in F3-F4 fibrosis
 - ELF of ≥ 9.8 is proposed as a measure of advanced liver fibrosis⁶
 - HA appears to be the major driver of the increase in ELF during progression to cirrhosis (Figure 1),⁷ due to dysfunction of sinusoidal epithelial cells, which normally metabolize serum HA⁸
- ELF is reduced by 5-6% in some MASH studies and is MOA dependent; several liver-directed MASH therapies that reduce liver fibrosis reduce ELF moderately or nonsignificantly,⁹⁻¹¹ while others (eg, GLP-related) significantly decrease ELF, irrespective of fibrosis stage, in F2-F3 and F0-F1 MASH¹²⁻¹⁹

FIGURE 1. ELF and ELF components by fibrosis stage^{7,a}



^aFrom an analysis correlating baseline ELF score with fibrosis stage in patients from phase 3 resmetirom trials. Data is presented as mean±SE.

- Weight loss (WL) has been shown to reduce liver stiffness and collagen markers in patients without significant liver fibrosis (F0-F1) who have obesity/metabolic risk, in whom serum markers of fibrosis may be elevated²⁰⁻²²
- Here, we examined the impact of ≥ 5% weight loss on VCTE and ELF and the association of changes in VCTE and ELF with weight loss and biopsy-assessed fibrosis improvement in resmetirom- and placebo-treated patients with MASH with F0-F1 and F2-F3 fibrosis from phase 3 MAESTRO trials

METHODS

- Adults with MASH with F0-F1 fibrosis from MAESTRO-NAFLD-1 (NCT04197479) and with F2-F3 fibrosis from MAESTRO-NASH (NCT03900429) were included in the analysis
- VCTE, ELF, and ELF components were assessed at baseline and Week 52 in both studies
- Liver biopsies were performed at baseline and Week52 in MAESTRO-NASH
- In MAESTRO-NASH (F2-F3) linear and logistic regression models were used to explore the associations between resmetirom- and placebo-mediated changes in both VCTE (log-transformed) and ELF (absolute) and:
 - Weight loss (≥ 5% vs < 5%)
 - Histologic fibrosis improvement

RESULTS

Associations of Changes in ELF, Liver Stiffness (VCTE) Weight Loss, in the F0-F1 Population

- Resmetirom did not significantly reduce ELF compared with placebo in the overall F0-F1 population¹⁰
- Approximately 14% of patients in the F0-F1 population had ≥ 5% WL at Week 52; ELF score showed greater reduction in those with ≥ 5% WL, with the P3NP component showing the greatest reduction in patients with WL, independent of treatment (Figure 2)
 - P3NP is the major fibrogenesis biomarker in ELF²³
- In F0-F1 baseline VCTE was mean 7.4 kPa median, 6.5 kPa
- Resmetirom did not significantly reduce VCTE compared with placebo in the MAESTRO-NAFLD-1 F0-F1 population¹⁰
- VCTE was significantly reduced in those with ≥ 5% weight loss versus those with < 5% weight loss independent of treatment (Figure 3)

FIGURE 2. Median P3NP % changes at Week 52 (F0-F1 population)

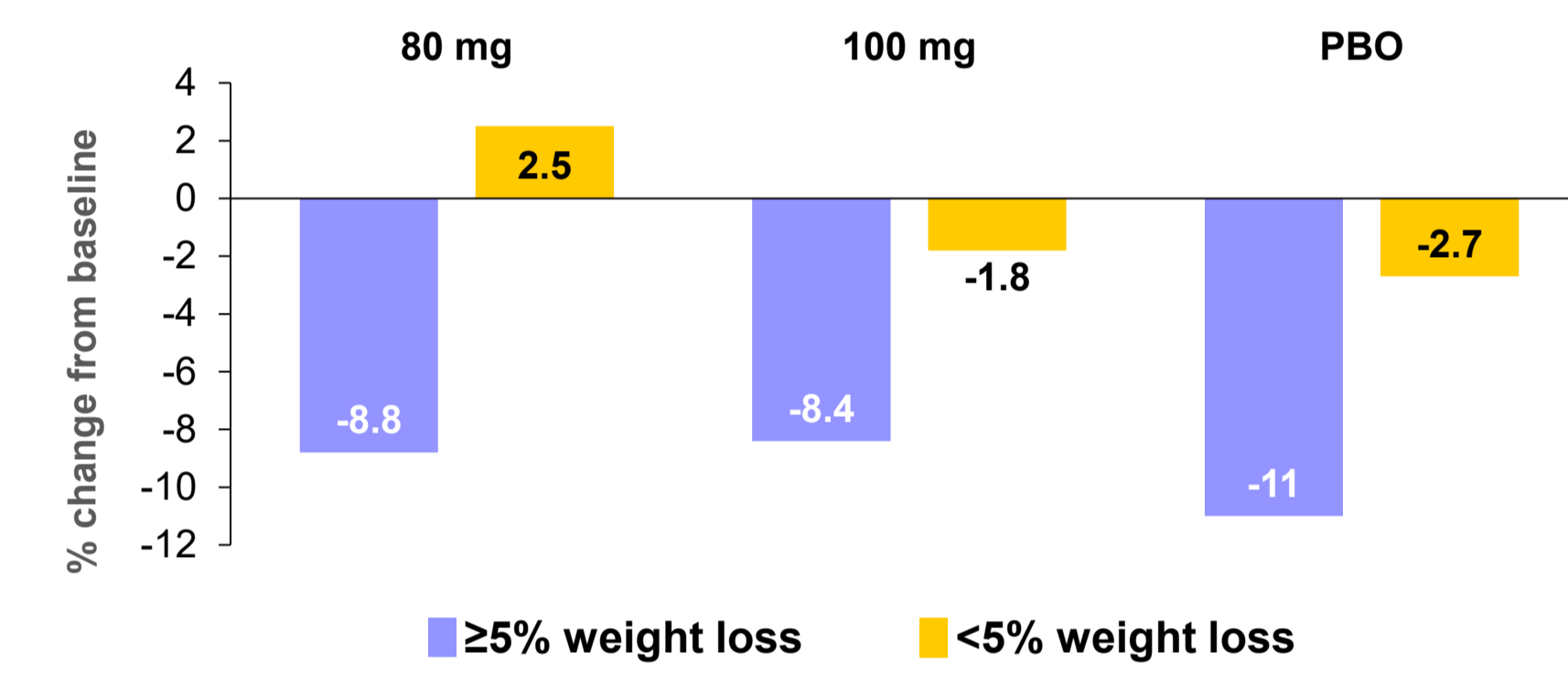
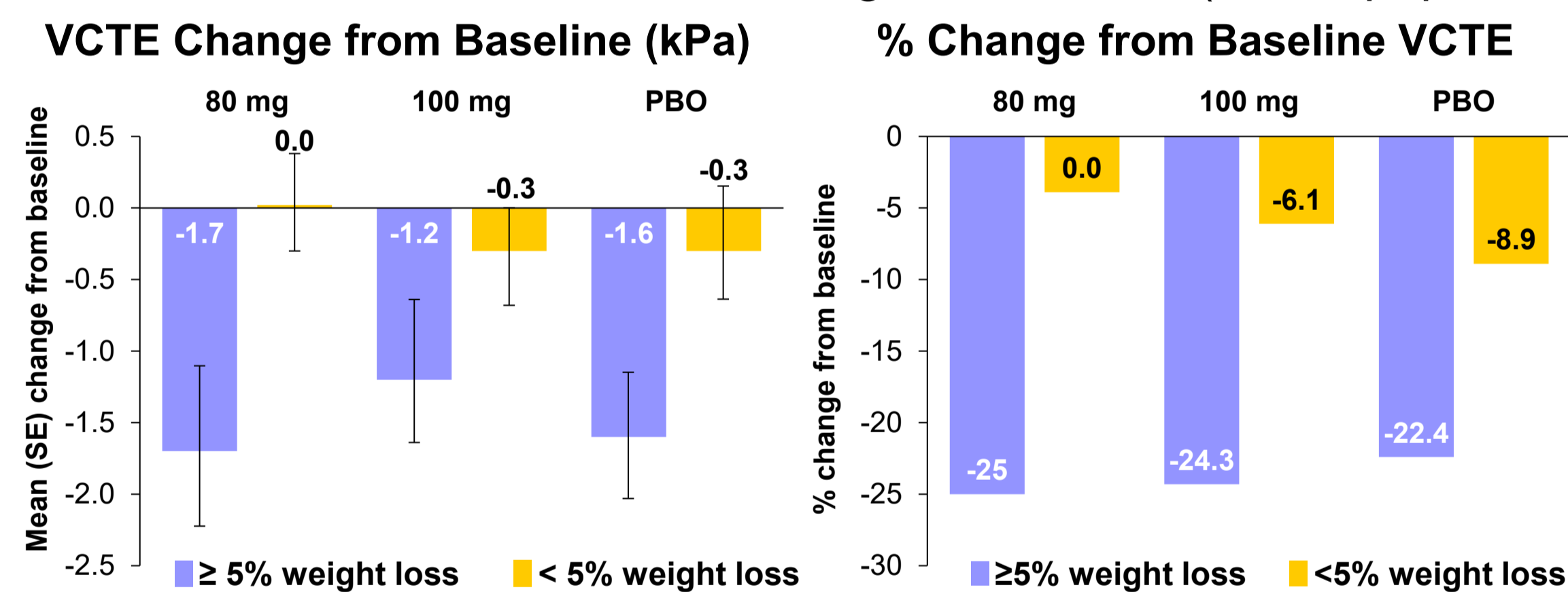


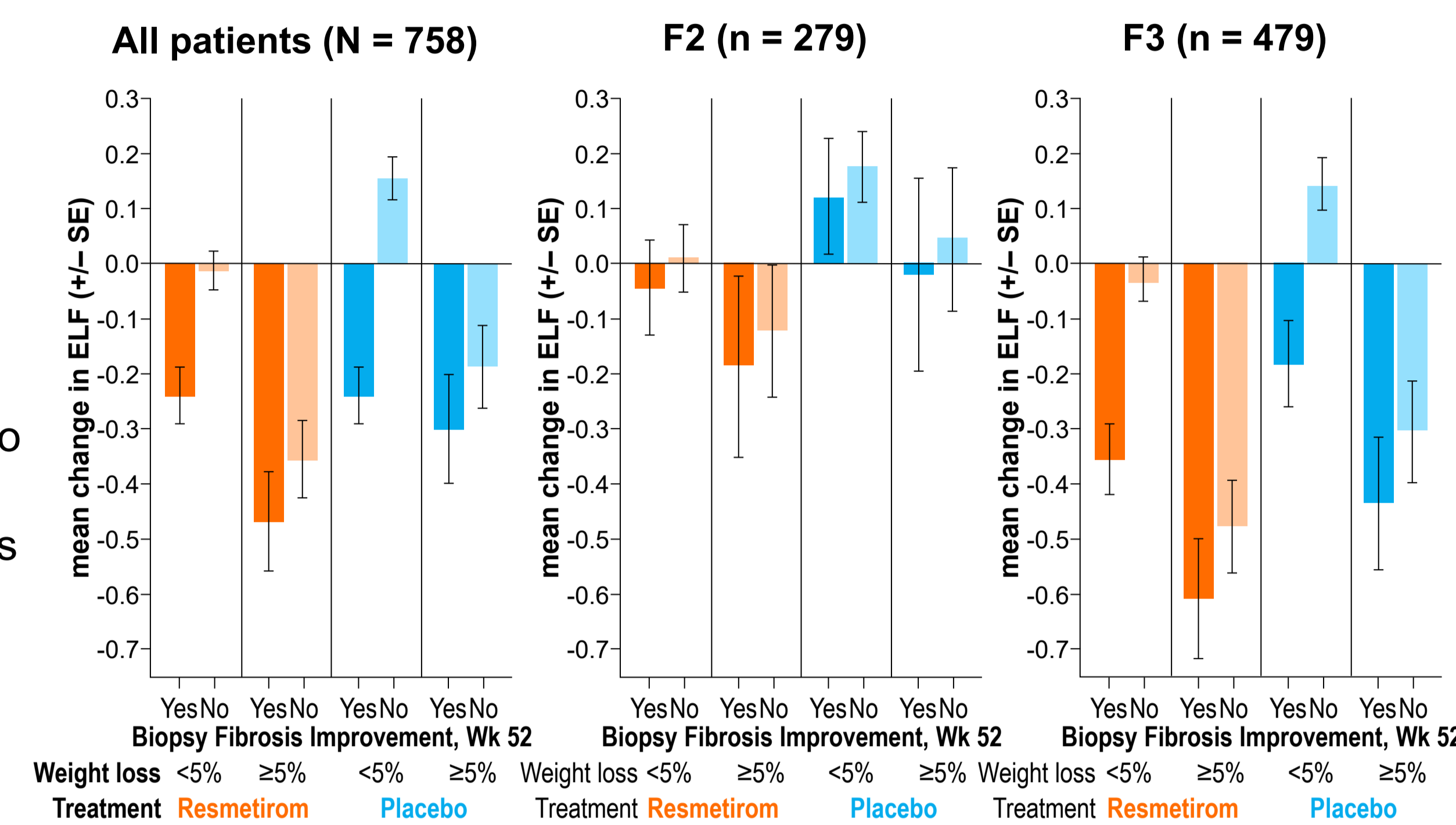
FIGURE 3. Mean and % VCTE change at Week 52 (F0-F1 population)



Associations of Changes in ELF, Liver Stiffness (VCTE) Weight Loss, and Fibrosis Improvement on Biopsy in the F2-F3 Population

- In the F2-F3 population, mean baseline ELF score was 9.8
- At Week 52, 17% (80mg resmetirom), 22% (100mg resmetirom) and 12% (PBO) had ≥ 5% WL
- Absolute changes in ELF were evaluated using observed and modeled data from a cohort of 758 patients with F2-F3 fibrosis (MAESTRO-NASH) with paired fibrosis, weight, and ELF data
- There were independent associations of WL and FI with changes in ELF, and associations of change in ELF with WL were more pronounced than associations of change in ELF with FI; most noticeable effects were observed in the F3 population (Figure 4)
- Interaction statistics showed that the effect of ≥ 5% WL on ELF attenuated a significant relationship between ELF and FI that was observed in resmetirom and placebo-treated patients with < 5% WL (Table 1, Figure 5)
- The association of change in ELF with fibrosis improvement was more pronounced in those with < 5% WL versus those with ≥ 5% WL (Figure 5)
- Changes in ELF were strongly associated with fibrosis improvement only in patients with F3 fibrosis with < 5% weight loss (Figure 5)

FIGURE 4. Absolute changes in ELF (F2-F3) (N = 758 with paired fibrosis/weight/ELF data) *



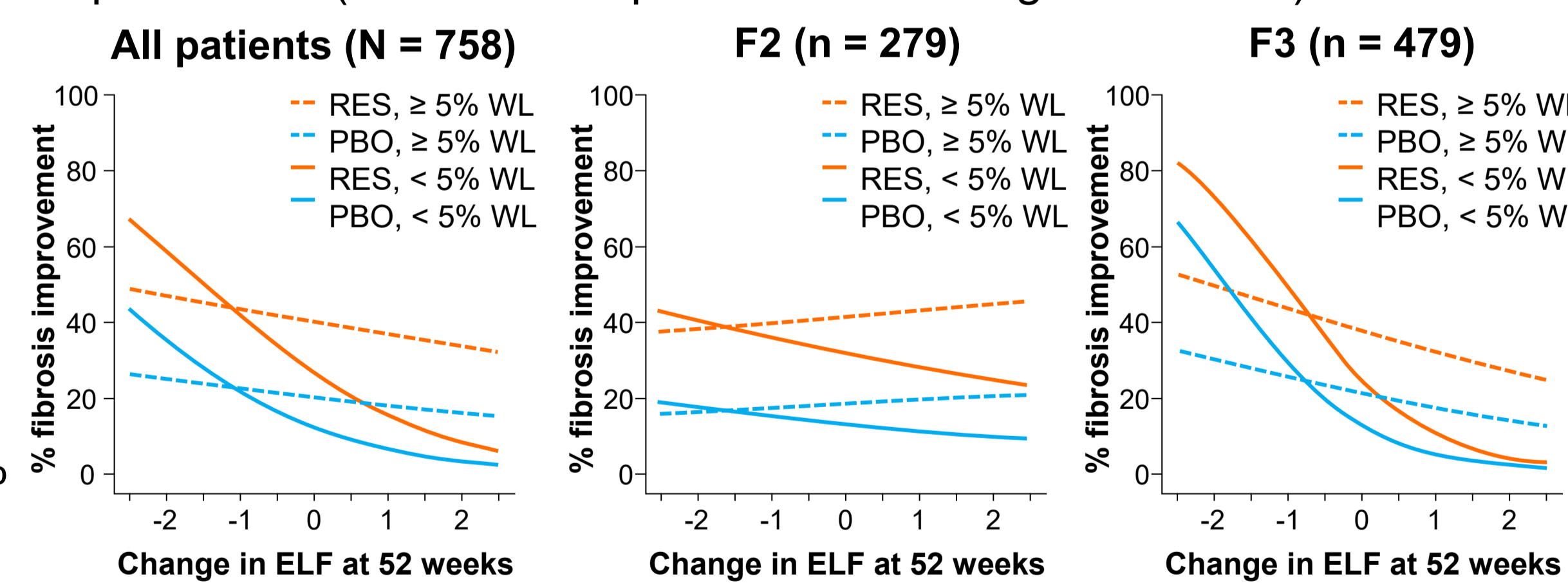
*Based on modeled data from linear regression: Change in ELF ~ Treatment + WL (WL, ≥ 5% vs < 5%) + FI at Week 52 (FI, Y/N) + WL x FI

TABLE 1. Modeled Associations on Fibrosis Improvement, binary change in weight, and changes in ELF

Predictor	All Patients		F2		F3	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Intercept	3.945	0.0012	-0.751	0.7305	6.524	0.0001
Treatment	0.973	< 0.0001	1.157	0.0005	0.839	0.0020
BL ELF	-0.538	< 0.0001	-0.088	0.6860	-0.776	< 0.0001
BL Weight	-0.007	0.0993	-0.003	0.6074	-0.009	0.0995
≥ 5% WL (vs < 5%)	0.588	0.0138	0.414	0.2711	0.660	0.0405
Δ ELF	-0.686	< 0.0001	-0.182	0.4451	-1.071	< 0.0001
≥ 5% WL x Δ ELF	0.546	0.0956	0.255	0.6622	0.821	0.0520

*Based on multivariate logistic regression: logit(Prob(FI)) ~ Res/Pbo + BL ELF + BL Weight + ≥ 5% WL + Δ ELF (≥ 5% WL x Δ ELF)

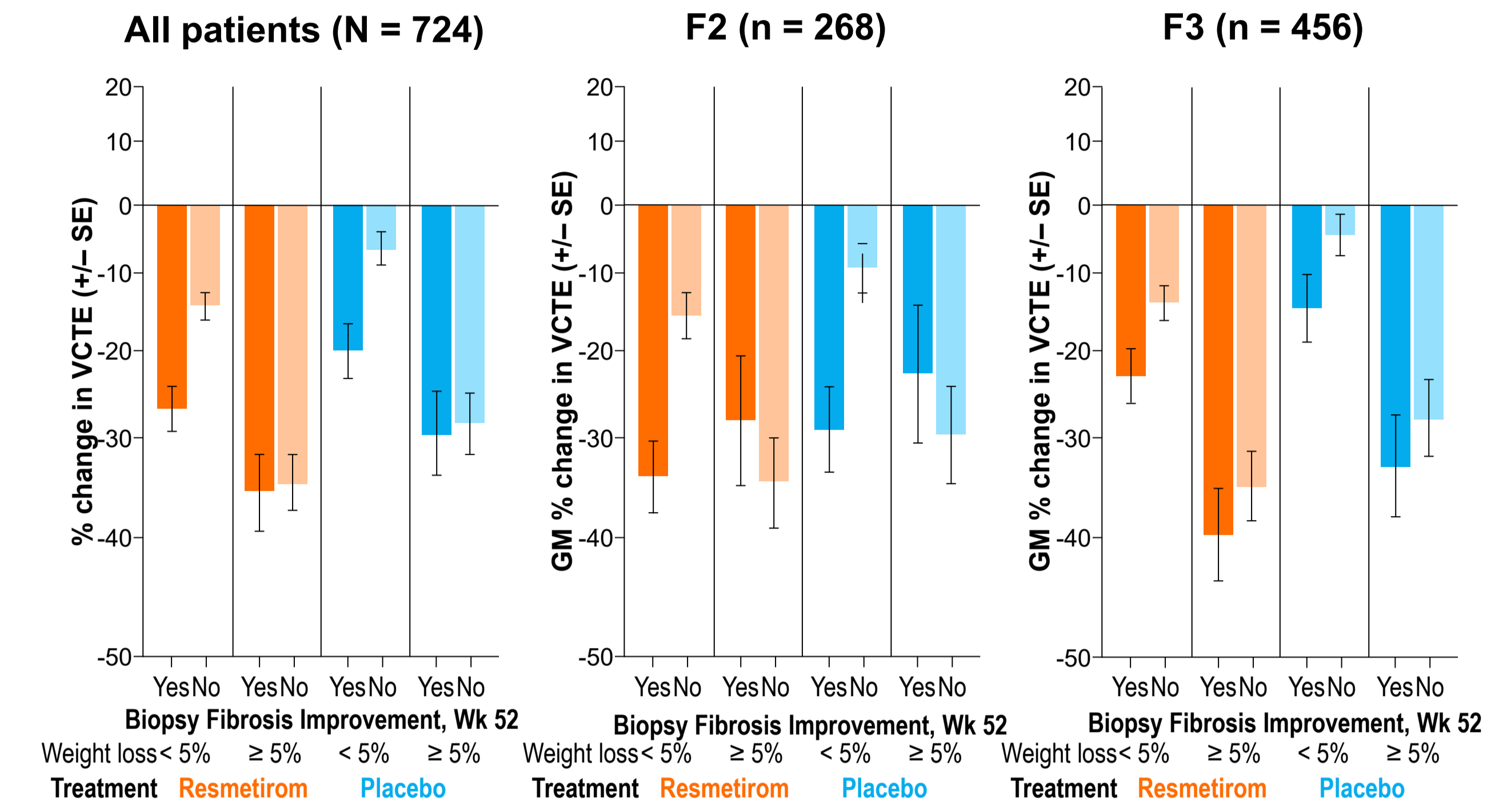
FIGURE 5. Effects of weight loss and changes in ELF on fibrosis improvement (N = 758 with paired fibrosis/weight/ELF data) *



*Based on modeled data from logistic regression: Probability FI ~ Treatment + WL (WL, ≥ 5% vs < 5%) + Change in ELF + WL x Change in ELF

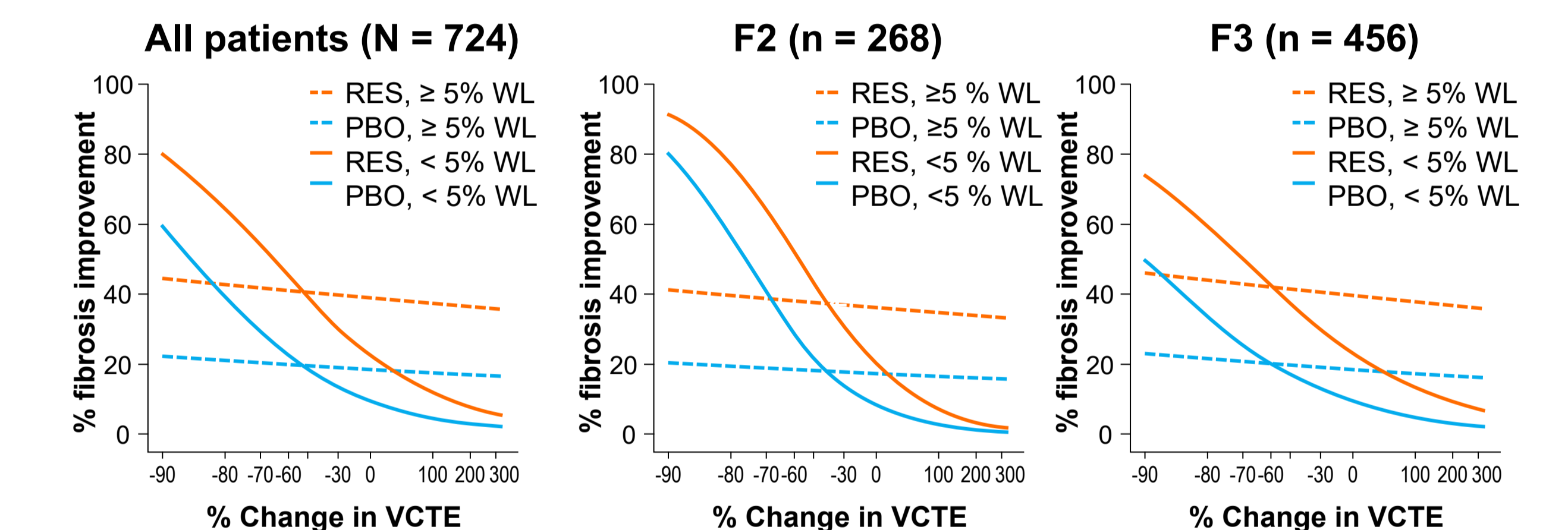
- In F2-F3 baseline VCTE was 13.3 kPa
- Relative changes in VCTE were evaluated using observed and modeled data from a cohort of 724 patients with F2-F3 fibrosis (MAESTRO-NASH) with paired fibrosis, weight, and VCTE data
- There were independent associations of WL and FI with changes in VCTE, and associations of change in VCTE with WL were more pronounced than associations of change in VCTE with fibrosis improvement (Figure 6)
- The association of VCTE with fibrosis improvement was pronounced in those with < 5% WL versus those with ≥ 5% WL in both resmetirom and placebo treated patients (Figure 7)
- Change in liver stiffness by VCTE predicted fibrosis improvement on biopsy in both F2 and F3 patients without weight loss (Figure 7)

FIGURE 6. Percent changes in VCTE (F2-F3) (N = 724 with paired fibrosis/weight/VCTE data) *



*Based on modeled data from linear regression: log(Fold Change in VCTE) ~ Treatment + WL (WL, ≥ 5% vs < 5%) + FI at Week 52 (FI, Y/N) + WL x FI

FIGURE 7. Effects of weight loss and percent changes in VCTE on Fibrosis improvement (N = 724 with paired fibrosis/weight/VCTE data) *



*Based on modeled data from logistic regression: Probability FI ~ Treatment + WL (WL, ≥ 5% vs < 5%) + log(Fold Change in VCTE) + WL x log(Fold Change in VCTE)

CONCLUSIONS

- In patients with F2-F3 MASH, weight loss ≥ 5% and fibrosis improvement independently associated with reductions in VCTE and ELF
- Fibrosis improvement was clearly associated with VCTE and ELF reduction in patients without weight loss treated with resmetirom or placebo
- Confounding effects of weight loss on ELF and VCTE, independent of histologic fibrosis improvement, should be considered when evaluating MASH treatments

ABBREVIATIONS

BL, baseline; ELF™, Enhanced Liver Fibrosis test; EU, European Union; FI, fibrosis improvement; GLP, glucagon-like peptide; GM, geometric mean; HA, hyaluronic acid; MASH, metabolic dysfunction-associated steatohepatitis; MOA, mechanism of action; N, no; P3NP, amino terminal of type III procollagen peptide; PBO, placebo; RES, resmetirom; SE, standard error; THR-β, thyroid hormone receptor-beta; TIMP-1, tissue inhibitor of metalloproteinase-1; VCTE, vibration controlled transient elastography; WK, Week; WL, weight loss; Y, yes.

DISCLOSURES AND ACKNOWLEDGEMENTS

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