Predictors of Frequency and Severity of Vasomotor Symptoms: Results from the REPLENISH Trial
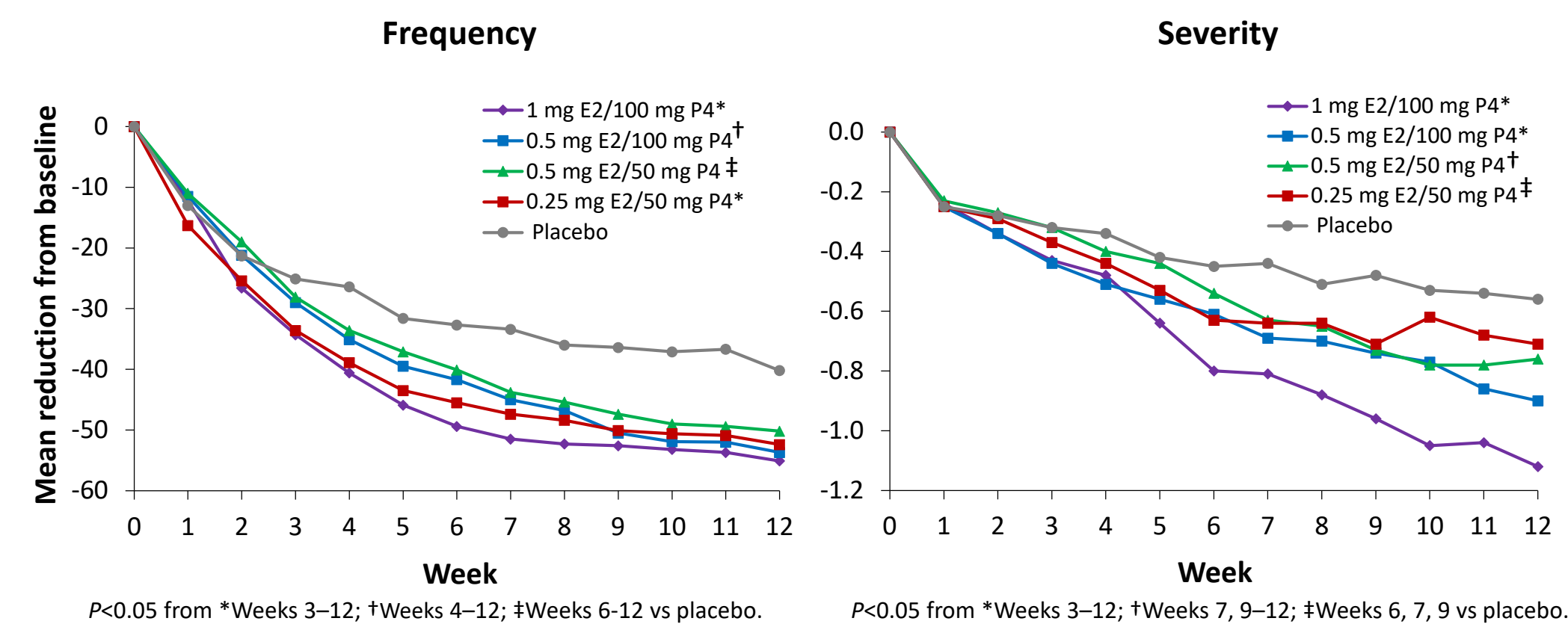
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Introduction

- Vasomotor symptoms (VMS) are a common complaint of postmenopausal women[1,2]
  - Moderate to severe VMS can be effectively treated with FDA-approved hormone therapy (HT)[3]
- The phase 3 REPLENISH trial evaluated four daily oral doses of E2/P4 capsules in postmenopausal women with a uterus; the primary efficacy and safety endpoints have been reported[4]
  - E2/P4 reduced the frequency and severity of moderate to severe hot flushes (**Figure 1**)[4] and improved quality of life outcomes,[5] while protecting the endometrium[4]

Figure 1. Weekly improvement in frequency and severity of moderate to severe VMS[4]

P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.

P<0.05 from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.

Objective

To determine whether baseline characteristics can predict the frequency and severity of hot flushes in postmenopausal women of the REPLENISH trial

Methods

Study Design

- The REPLENISH trial (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated the safety and efficacy of four E2/P4 doses in postmenopausal women with a uterus[4]
- Women with moderate to severe hot flushes (≥7/day or ≥50/week) were included in a VMS substudy and were randomized to daily oral E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, or 0.25/50, or placebo for 12 months; other women were randomized to the active E2/P4 doses only[4]

- Eligible women had a uterus and were between the ages of 40 and 65 years, postmenopausal, and seeking treatment for menopausal VMS[4]
- Women were included in the modified intent-to-treat (MITT)-VMS population if they were randomized to the VMS substudy, had hot flush frequency and severity data at baseline and for at least one on-treatment week

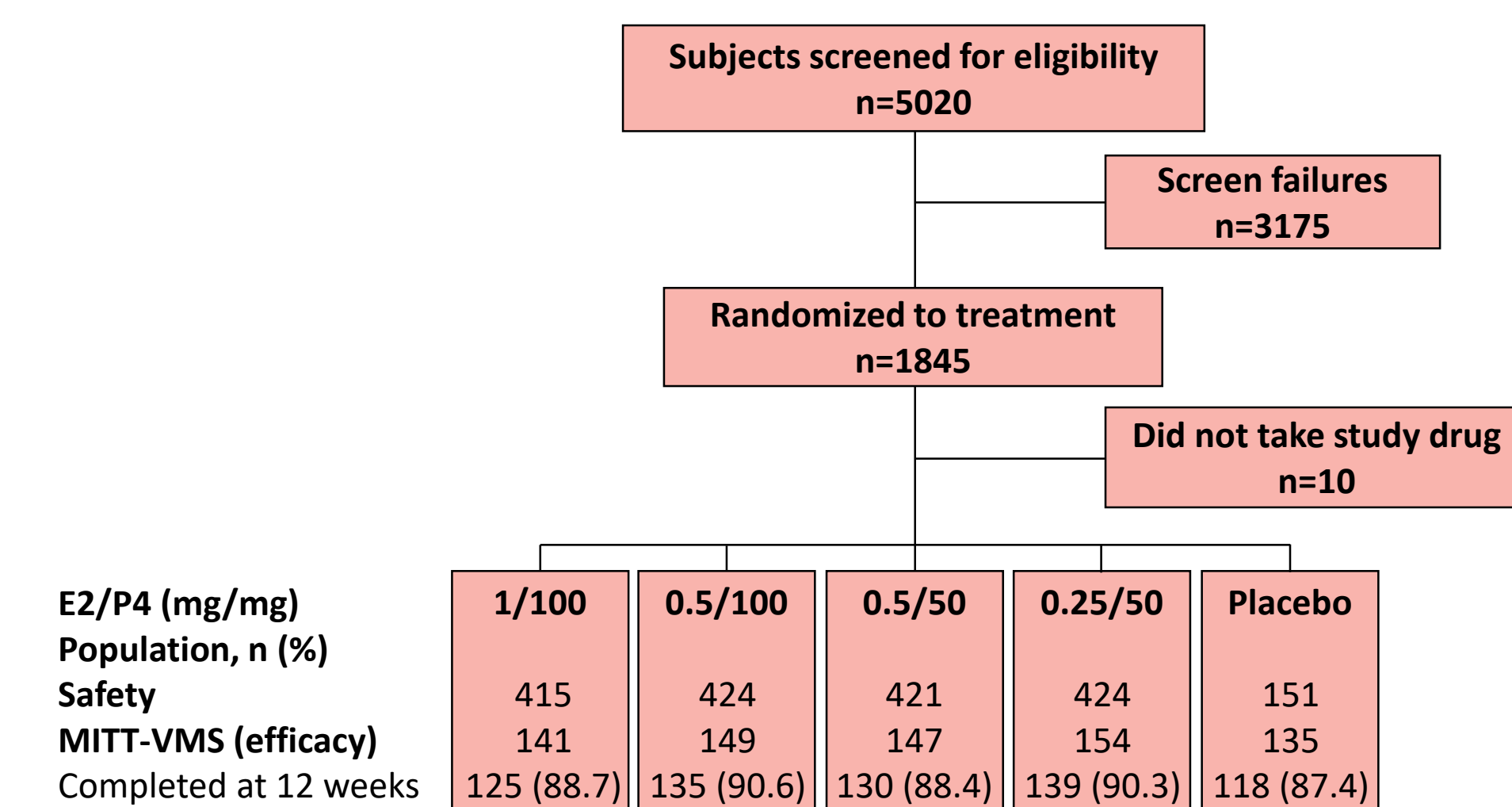### Predictors of Baseline VMS Frequency and Severity

- The impact of baseline characteristics, including age, race, body mass index (BMI), smoking, time since last menstrual period (LMP), age at LMP, tubal ligation, parity, estradiol concentration, and menopause-specific quality of life (MENQOL) total and vasomotor domain scores, was assessed by post hoc analyses on the frequency and severity of hot flushes
  - Univariate associations and multivariate logistic regressions were used to determine predictors for having ≥50 moderate to severe hot flushes per week
  - Univariate and multivariate logistic regressions were used to determine predictors of hot flush severity

Results

Study Disposition and Demographics

- A total of 1845 women were randomized; 726 were included in the MITT-VMS population (**Figure 2**)
- Women in the VMS substudy had a mean age of 55 years (range, 40-65 years) and mean BMI of 27 kg/m^{2}; 67% were white and 31% were African American

Figure 2. Patient disposition

E2/P4 (mg/mg)	1/100	0.5/100	0.5/50	0.25/50	Placebo
Population, n (%)					
Safety	415	424	421	424	151
MITT-VMS (efficacy)	141	149	147	154	135
Completed at 12 weeks	125 (88.7)	135 (90.6)	130 (88.4)	139 (90.3)	118 (87.4)

Predictors of Baseline VMS Frequency and Severity

- Significant predictors for having ≥50 moderate to severe hot flushes per week were BMI, MENQOL total score, and MENQOL vasomotor domain score (**Table 1**)
  - One-unit increase in BMI decreased the odds by 13%
  - One-point increase in MENQOL total score (worsening) increased the odds by 21%
  - One-point increase in MENQOL vasomotor score (worsening) increased the odds by 111%
- Multivariate logistic regression showed that BMI and the MENQOL total score or vasomotor domain score were independent predictors of VMS frequency
- Age, race, smoking, time since LMP, age at LMP, tubal ligation, parity, and baseline E2 did not significantly predict having ≥50 moderate to severe hot flushes per week

Table 1. Predictors for having ≥50 moderate to severe hot flushes/week

Parameters		OR (95%CI)	P-values
Age, y	5-year increase	1.00 (0.90–1.12)	0.949
Race	Black vs white	0.90 (0.74–1.10)	0.772
	Other vs white	0.90 (0.49–1.65)	0.858
BMI, kg/m^{2}	1-unit increase	0.87 (0.77–0.99)	0.030
Smoking	Current vs never	1.06 (0.84–1.33)	0.366
	Former vs never	0.91 (0.73–1.14)	0.278
Time since LMP	1-year increase	1.01 (0.99–1.03)	0.320
Age at LMP	1-year increase	0.96 (0.86–1.06)	0.437
Tubal ligation	No vs yes	1.01 (0.83–1.23)	0.899
Parity	No vs yes	1.07 (0.82–1.38)	0.627
Baseline E2 levels, pg/mL	1-unit increase	0.99 (0.98–1.01)	0.229
MENQOL, score			
Total	1-point increase	1.21 (1.13–1.30)	<0.0001
Vasomotor domain	1-point increase	2.11 (1.92–2.32)	<0.0001

BMI, body mass index; CI, confidence interval; E2, estradiol; LMP, last menstrual period; MENQOL, menopause-specific quality of life; OR, odds ratio; VMS, vasomotor symptoms.

- Baseline predictors for increased hot flush severity were current smoking, and MENQOL total and vasomotor scores (**Table 2**)
- Multiple regression analyses showed that the MENQOL vasomotor score was the best predictor of severity (R^2=0.1876; P<0.0001), followed by MENQOL total score plus smoking (R^2=0.0325; P<0.0001)
- Other baseline characteristics evaluated were not predictors of hot flush severity

Table 2. Predictors of VMS severity

Parameters		Estimate ± SE	P-value
Age, y	5-year increase	-0.002 ± 0.01	0.847
Race	Black vs white	0.005 ± 0.02	0.824
	Other vs white	-0.058 ± 0.07	0.389
BMI, kg/m^{2}	1-unit increase	-0.002 ± 0.01	0.909
Smoking	Current vs former	0.088 ± 0.03	0.003
	Current vs never	0.061 ± 0.03	0.018
	Current vs former/never	0.070 ± 0.02	0.004
	Former vs never	-0.027 ± 0.03	0.291
Time since LMP	1-year increase	0.002 ± 0.002	0.441
Age at LMP	1-year increase	-0.010 ± 0.012	0.397
Tubal ligation	No vs yes	0.002 ± 0.022	0.919
Parity	No vs yes	-0.028 ± 0.029	0.333
Baseline E2 levels, pg/mL	1-unit increase	0.002 ± 0.002	0.299
MENQOL, score			
Total	1-point increase	0.058 ± 0.008	<0.0001
Vasomotor domain	1-point increase	0.142 ± 0.007	<0.0001

BMI, body mass index; CI, confidence interval; E2, estradiol; LMP, last menstrual period; MENQOL, menopause-specific quality of life; OR, odds ratio; VMS, vasomotor symptoms.

Conclusions

- Women with lower BMI and/or higher MENQOL total and vasomotor domain scores were more likely to have ≥50 moderate to severe hot flushes per week
- Current smokers and those with high MENQOL total and vasomotor domain scores were more likely to have more severe hot flushes
- These characteristics could potentially be used clinically to predict women's hot flush frequency and severity at menopause

References

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Disclosures